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THE FASCINATING CHEMISTRY OF MESOIONIC 4-TRIFLUOROACETYL-1,3-OXAZOLIUM-5-OLATES AND RELATED COMPOUNDS

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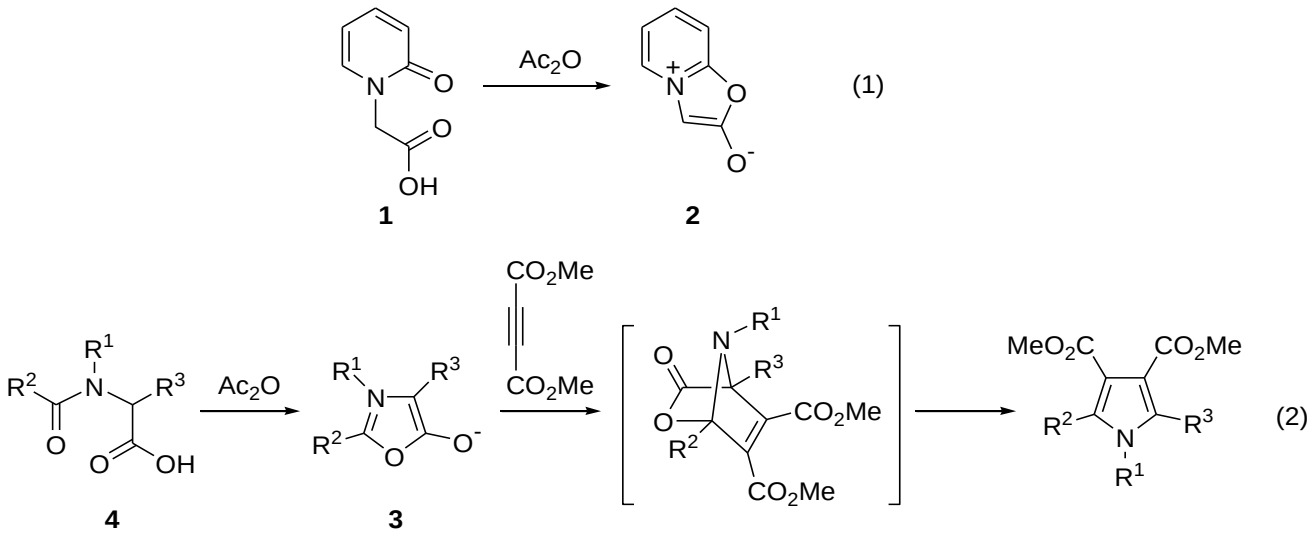
Abstract – This review illustrates the unexpected and unique transformation of mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates (4-TFMK-münchnones) on treatment with different nucleophiles. A trifluoromethyl group that cannot be synthesized by the usual methods is incorporated in the products. The research discussed in this review is focused on the rich chemistry of 4-TFMK-münchnones. In particular, we highlight the recent advances in their use in contemporary organic synthesis, primarily of trifluoromethyl-substituted heterocycles. The chemistry of related mesoionic compounds is also discussed.

CONTENTS

1. INTRODUCTION

Mesoionic 1,3-oxazolium-5-olate (münchnone) derivative **2** was first synthesized in 1958 by Lawson and Miles[1] by cyclodehydration of 2-pyridone-*N*-acetic acid **1** with acetic anhydride (Scheme 1, eq. 1). The 1,3-dipolar (azomethine ylide type) reactivity of münchnones **3** was originally discovered by Huisgen in 1964 (Scheme 1, eq. 2).[2] Since then, the Huisgen group has extensively studied the chemical properties, reactivity, and utility of münchnones **3**, the name of which was derived from Huisgen's Alma mater, the Ludwig-Maximilians-Universität München.

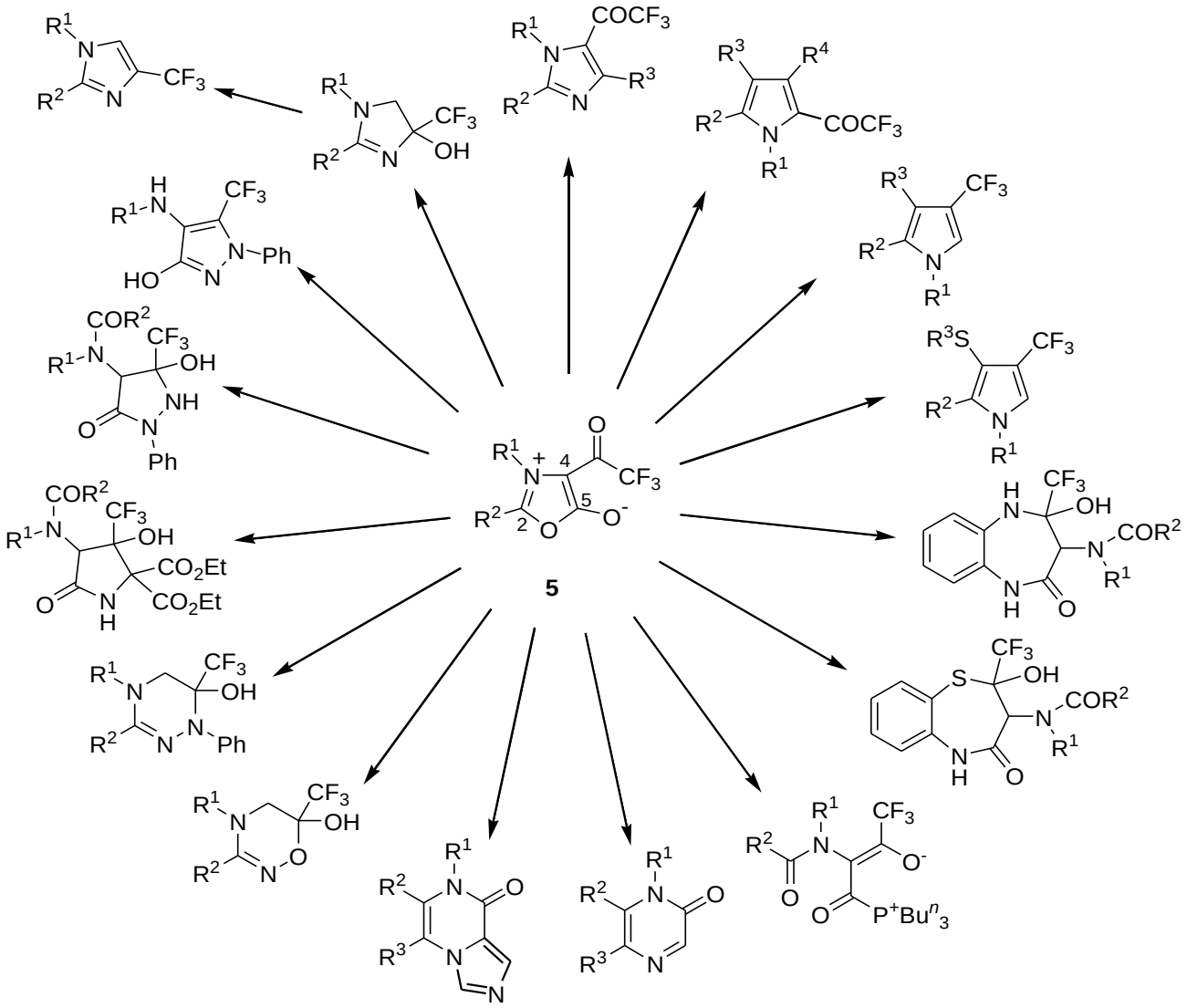


Scheme 1. Preparation of münchnones and their 1,3-dipolar cycloaddition reaction

Münchnones **3**, synthesized from *N*-alkyl(aryl)-*N*-acyl α-amino acids **4**, have received steady interest for more than 60 years. In particular, as they are highly reactive 1,3-dipoles, their 1,3-dipolar cycloadditions (known as the Huisgen cycloaddition) have been extensively studied.[3] Münchnones can undergo cycloaddition reactions with a range of unsaturated substrates (e.g. alkynes, alkenes, imines, and aldehydes), and this reactivity provides potential access to various classes of heterocycles.[4] Thus, münchnones, like sydnones,[5] are one of the most extensively studied classes of mesoionic compounds.[6]

A review by Gribble covering the syntheses, structures, and reactions of münchnones in the literature available up to 2000 appeared in 2003.[6] Recent new aspects of münchnone chemistry, mainly features regarding novel generation method for münchnones were reviewed by Reissig and Zimmer in 2014.[4]

The present article is a comprehensive survey of the chemistry of münchnones with trifluoroacetyl groups at the 4-position, mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates (4-TFMK-münchnones) **5**, based primarily on our research results.



Scheme 2. 4-TFMK-münchnones 5 in diversity-oriented synthesis

4-TFMK-münchnones **5** contain numerous reactive sites, allowing a diverse set of possible modifications (Scheme 2). Highly substituted heterocyclic scaffolds can be directly accessed from **5**. The diverse reactivity makes them useful synthons for trifluoromethyl-substituted heterocycles. Because of the strong influence of fluorinated groups on the physical, chemical, and biological properties of compounds and the

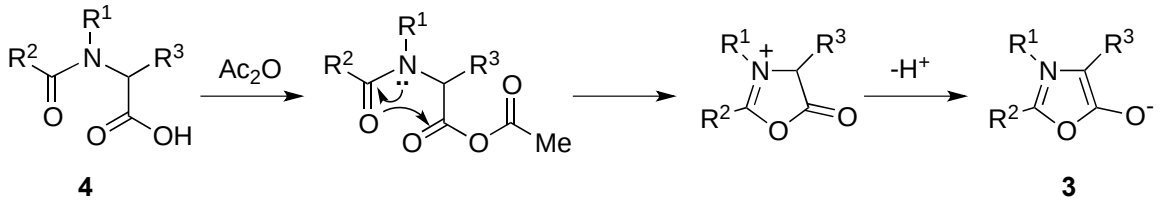
fact that a large majority of modern medicines and agrochemicals contain one or more heterocyclic rings, trifluoromethyl-substituted heterocycles are of high interest in medicinal, agrochemical, and materials chemistry.[7]

This review is intended to create a prognostic scheme to illustrate the unexpected and unusual transformations of **5** on treatment with different nucleophiles and to partially compare the results with those of non-acylated münchnones.

2. 4-TFMK-MÜNCHNONES AND RELATED MESOIONIC COMPOUNDS

2-1. Synthesis and properties of münchnones

Although the term "mesoionic" has been used to imply a variety of heterocyclic systems, such as six-membered heteroaromatic betaines and heteropentalenes, a consensus is growing that use of this term should be restricted to five-membered heterocycles.[8] This restriction excludes betaines, heteropentalenes, and five-membered heterocyclic *N*-oxides; however, it does not exclude five-membered rings fused to other heterocyclic systems. Münchnones have a sextet of π electrons and an aromatic character, but their properties and reactivities are very different from those of aromatic compounds. Whether or not münchnones are aromatic is still controversial.[9]

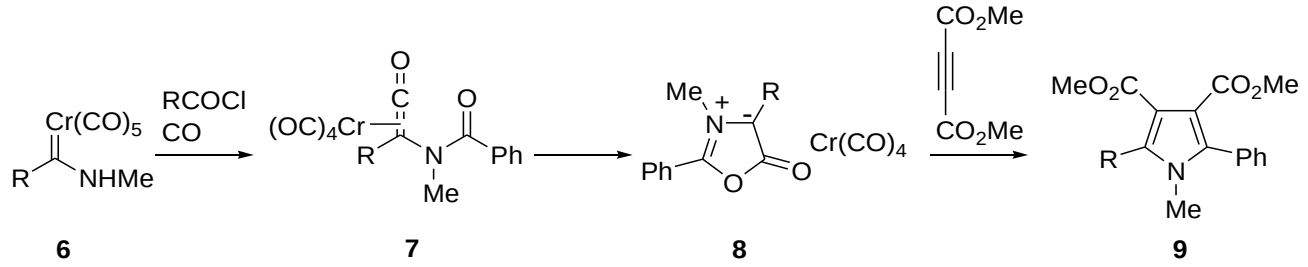


4 **3**

Scheme 3. Preparation of münchnones 3 from *N*-alkyl(aryl)-*N*-acyl α-amino acids 4

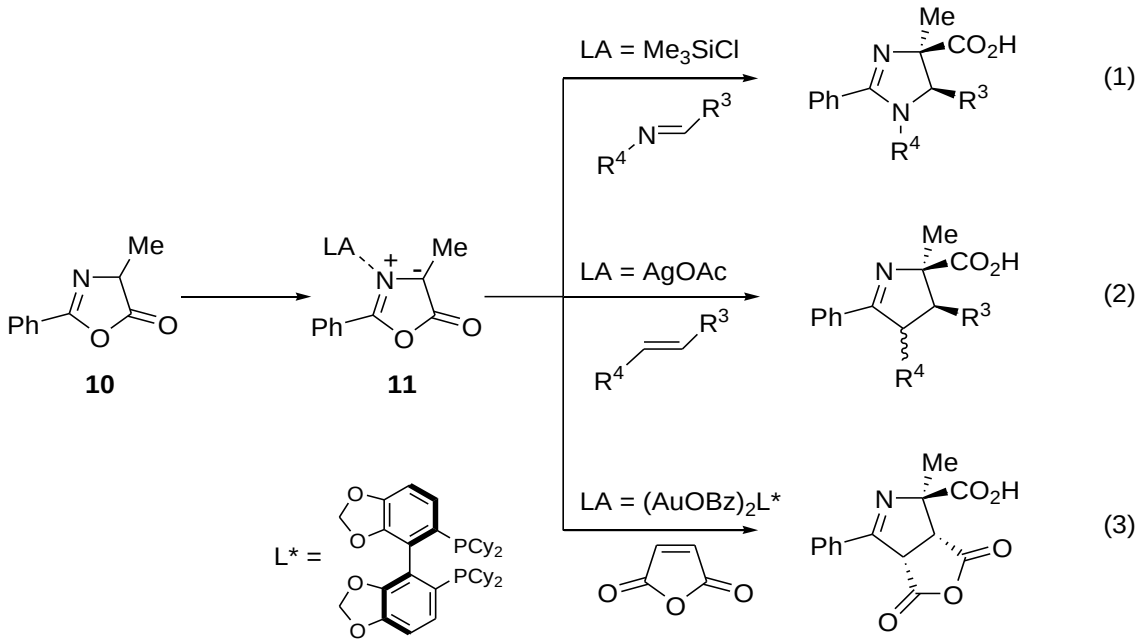
In general, münchnones **3** are readily prepared by cyclodehydration of *N*-alkyl(aryl)-*N*-acyl α-amino acids **4** with reagents such as acetic anhydride,[2] *N*,*N*'-dicyclohexylcarbodiimide (DCC),[10] or *N*-ethyl-*N*'-dimethylaminopropylcarbodiimide (EDC)[11] and are utilized *in situ* because they are too unstable to be isolated (Scheme 3). Only münchnones with aryl substituents at both the 2- and 4-positions or with an acyl group in the 4-position have been isolated.[2b]

Alternative approaches for the formation of münchnones have been reported. In 2000, the novel generation of münchnones from chromium carbene complexes **6** was reported by Merlic and co-workers.[12] Carbene complexes **6** react with carbon monoxide to yield chromium ketene complexes **7**, which cyclize to münchnones **8**; these are then converted into pyrroles **9** through 1,3-dipolar cycloaddition with alkynes (Scheme 4).



Scheme 4. Cyclization reactions of münchnones 8 generated from chromium carbene complexes 6

Tepe *et al*. reported the conversion of azlactones **10** by trimethylsilyl chloride (Scheme 5, eq. 1)[13] or silver acetate (Scheme 5, eq. 2)[14] into *N*-metalated münchnone intermediates **11** (LA=Me_3Si or Ag), which undergo a 1,3-dipolar cycloaddition in the presence of alkenes.

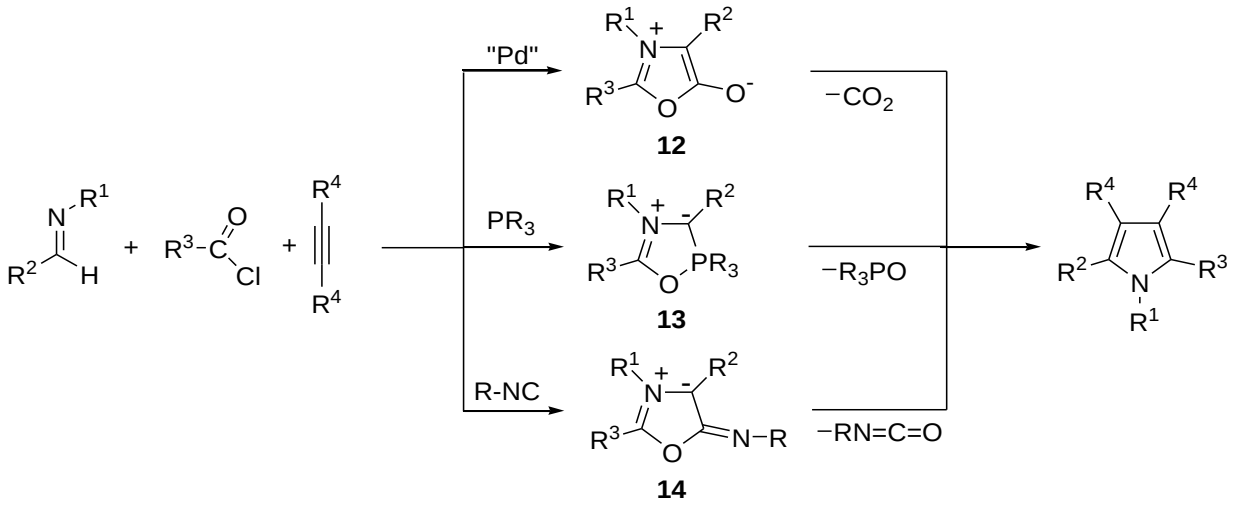


Scheme 5. Cyclization reactions of *N*-metalated münchnones 11 generated from azlactones 10

Toste *et al*. have also developed a gold-catalyzed conversion route of generating aura-münchnone intermediate **11** (LA = $(AuOBz)_2L^*$) from azlactones **10**.[15] Intermediate **11** (LA = $(AuOBz)_2L^*$) undergoes regio- and stereoselective 1,3-dipolar cycloadditions with alkenes (Scheme 5, eq. 3).

The Arndtsen group designed three new routes to generate münchnones by multicomponent reactions: (1) the palladium-catalyzed carbonylative coupling of imines, acid chlorides, and carbon monoxide to afford münchnones **12**;[16] (2) the one-pot reaction of imines, acid chlorides and phosphonites to give phospha-münchnones **13** (called montréalones);[17] and (3) the isocyanide-mediated reaction of imines and acid chlorides to afford imino-münchnones **14** (Scheme 6).[18] The 1,3-dipoles **12**-**14** can undergo

cycloaddition with alkynes and alkenes to produce a range of heterocyclic products. Montréalones **13** undergo regio- and enantioselective cycloaddition reactions because the PR_3 moiety in the ring increases the carbanionic character of the adjacent carbon atom and creates a steric bias across the 1,3-dipole.[17]



Scheme 6. Münchnones, montréalones, and imino-münchnones generated by one-pot reactions of imines and acid chlorides with either CO/Pd (for 12), PR_3 (for 13), or RNC (for 14)

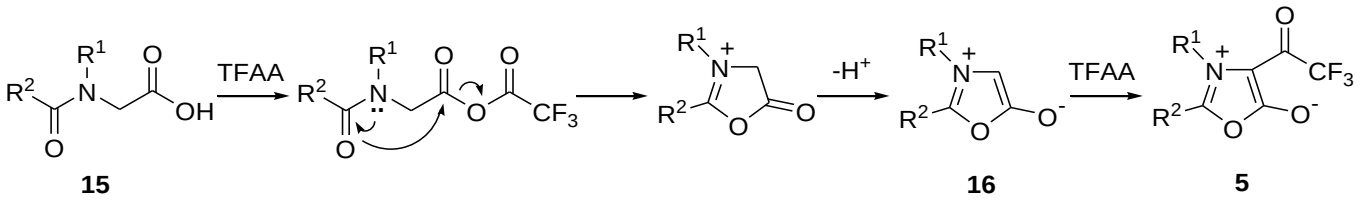
2-2. Synthesis and properties of 4-TFMK-münchnones and related mesoionic compounds

In 2014, Larock, Shi *et al*. used the term "stable münchnones" to refer to münchnones with electron-withdrawing groups at the 4-position.[19] Later, Harrity *et al*. also called them "stabilized münchnones".[20] These münchnones can be significantly more stable than their non-acylated analogs, allowing them to be isolated, purified and used as electrophiles and 1,3-dipoles.

Münchnones with trifluoroacetyl groups at the 4-position, 4-TFMK-münchnones **5**, were first synthesized in 1964 by Singh and Singh through the cyclodehydration of *N*-benzoyl-*N*-phenylglycine **15** (R^1=R^2=Ph).[21] In 1967, Greco *et al*. also reported experimental details of the preparation of additional 4-TFMK-münchnones **5** with spectral data.[22] The first reported reaction of **5** was the reactions with oxygen nucleophiles.[21] After 30 years, the synthetic utility of compounds **5** as valuable building blocks for the preparation of trifluoromethyl-substituted compounds was recognized when our group reported the reaction of **5** with amidines to afford 5-trifluoroacetylimidazoles (see Scheme 25).[23]

4-TFMK-münchnones **5** are easily prepared from *N*-acyl-*N*-alkylglycines **15** in one step through cyclodehydration by trifluoroacetic anhydride followed by trifluoroacetylation at the C-4 position of intermediary mesoionic 1,3-oxazolium-5-olates **16** (Scheme 7).[22] Generally, compound **5** can be isolated as crystalline materials and are reasonably stable on the bench top. Compounds with various substituents at the 2- and 3-positions can be synthesized. Of the compounds that we have synthesized, only the

2-methyl-3-phenyl-4-trifluoroacetyl derivative of **5** (R^1 = Ph, R^2 = Me) decomposed very slowly during storage in the refrigerator.



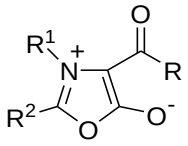
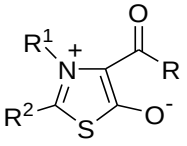
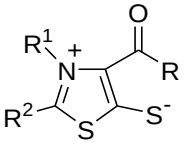
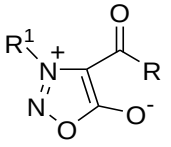
15 **16** **5**

R^1 = Me, Bn, Ph; R^2 = Me, *t*-Bu, Ph, 4-BrC_6H_5, 4-$MeOC_6H_5$

Scheme 7. Preparation of 4-TFMK-münchnones 5 from *N*-alkyl(aryl)-*N*-acyl α-amino acids 15

The preparation of 4-acetylmünchnones **17** has been described in three papers.[19,24a,b] Generally, compounds **17** are isolated and purified by recrystallization, whereas purification by column chromatography was generally problematic. Therefore, preparation of **17** with diverse substituents is difficult.[19] Conversely, acylation of 2-pyridone-*N*-acetic acid **1** with acyl chlorides or anhydrides leads to stable mesoionic 3-acyloxazolo[3,2-*a*]pyridinium-2-olates.[1,25] As far as we know, the synthesis of 4-formylmünchnones, among the related 4-acylmünchnones, has not been reported so far (Table 1).

Table 1. 4-Acyl mesoionic compounds

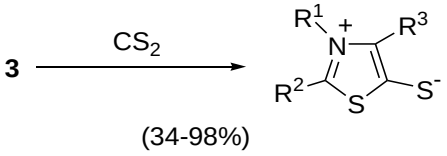
R				
CF_3	**5**[a]	**18**[c]	–	**21**[e]
CH_3	**17**[b]	**19**[d]	–	**22**[f]
H	–	**20**[c]	–	**23**[g]

[a] ref. 21 and 27. [b] ref.19 and 24. [c] ref. 26. [d] ref. 27. [e] ref. 34. [f] ref. 32. [g] ref. 31.

4-Acyl-1,3-thiazolium-5-olate derivatives, such as those with trifluoroacetyl (**18**),[26] acetyl (**19**),[27] and formyl (**20**)[26] substituents, are known compounds. However, their chemistry has not yet attracted much attention.

In 1967, the Huisgen group pioneered cycloaddition reactions of münchnones **3** with carbon disulfide to afford 1,3-thiazolium-5-thiolates (Scheme 8).[28] The mesoionic compounds have attracted special attention as nonlinear optical materials because of their large optical hyperpolarizabilities.[29] However, 4-acyl-1,3-thiazolium-5-thiolate derivatives have not yet been synthesized (Table 1). In addition, our

attempted preparation of 4-trifluoroacetyl-1,3-thiazolium-5-thiolates by the cycloaddition of **5a** (R^1 = Me, R^2 = Ph) with CS_2 was not successful.[30]

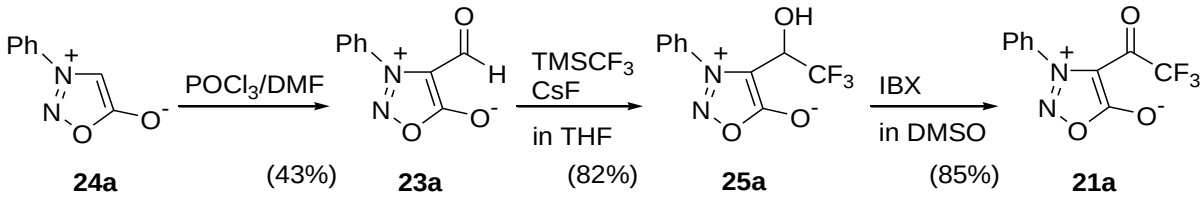


R^1 = Me; R^2 = 4-ClC_6H_4, 4-FC_6H_4, 4-$CF_3C_6H_4$, 4-$NO_2C_6H_4$, 4-$MeOC_6H_4$;

R^3 = Ph, 4-MeC_6H_4, 4-$Me_2CHC_6H_4$, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$

Scheme 8. Cycloaddition of münchnones 3 with CS_2 to give 1,3-thiazolium-5-thiolates

Sydnone derivatives substituted with an acyl group at the 4-position were reported to be stable compounds. 4-Formyl- (**23**)[31] and 4-acetylsydnones (**22**)[32] were obtained by direct acylation of 4-unsubstituted sydnones **24**, whereas 4-trifluoroacetylsydnones **21** were not synthesized by direct trifluoroacetylation.[33] In 2017, 4-trifluoroacetyl-3-phenylsydnone **21a** (R^1 = Ph) was first synthesized from 3-phenylsydnone **24a** (R^1 = Ph) by trifluoromethylation of 4-formyl-3-phenylsydnone **23a** (R^1 = Ph) with trifluoromethyltrimethylsilane followed by oxidation with *o*-iodoxybenzoic acid (IBX) of the corresponding trifluoromethyl alcohol **25a** (R^1 = Ph) (Scheme 9).[34] In the design of bioactive sydnones, hybrid molecules of sydnones and other heterocycles such as imidazoles have been synthesized from 4-formylsydnones **23** as an attractive starting material.[35] The Schmidt reaction of 4-acetylsydnones **22** with sodium azide and sulfuric acid afforded sydnonyl-methylamides.[36]



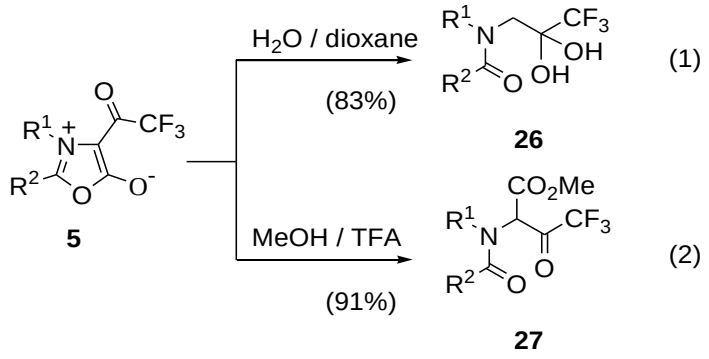
Scheme 9. Preparation of 4-trifluoroacetyl-3-phenylsydnone 21

However, there is much less information about the reactivity of 4-acylated mesoionic 1,3-thiazolium-5-olates, 1,3-thiazolium-5-thiolates, and sydnones in the literature in comparison with 4-TFMK-münchnones **5**.

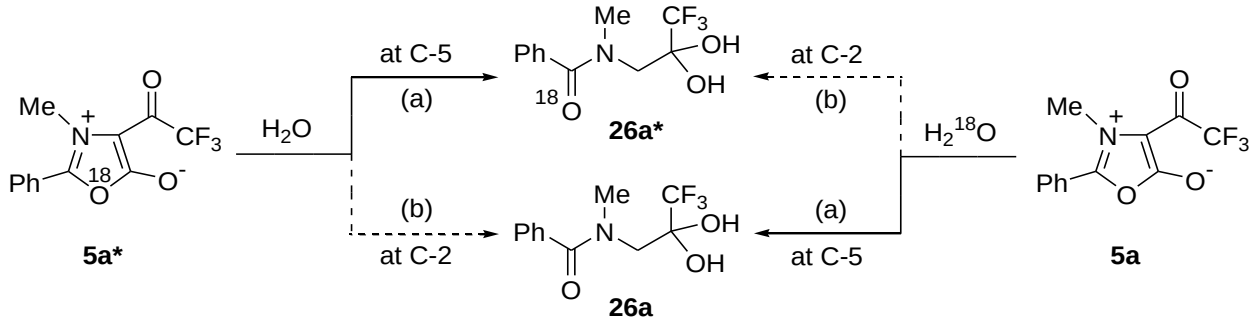
3. CHEMICAL REACTIONS

3-1. Ring-opening reaction

With regard to the electrophilic sites of **5**, H_2O and ethanol attack at the C-5 position.[21] Hydrolysis of **5** with H_2O results in decarboxylation and the formation of trifluoromethyl ketone hydrates **26** (Scheme 10, eq. 1). Alcoholysis of **5** gives the ring opening products **27** in high yields (Scheme 10, eq. 2). However, an alternative mechanism, in which *O*-nucleophiles such as H_2O and MeOH attack at the C-2 position of **5**, has not been ruled out from a comparison of the starting compound and the product. As described in a later section (see Scheme 27), aminolysis of **5** with ammonia proceeds by initial attack at the C-2 position of **5**, followed by ring opening, decarboxylation, and cyclization to give 4,5-dihydroimidazoles.[37] One distinguishing feature between the two possible mechanisms of ring opening of **5** is the source of the oxygen on the amide of product **26** in the case of an attack of *O*-nucleophiles at C-5 (pathway a) and at C-2 (pathway b) (Scheme 11). By performing the reactions of ^{18}O-labeled **5a*** with H_2O and **5a** with $H_2{}^{18}O$, it should be possible to obtain direct evidence regarding the site of the nucleophilic attack on **5**.[38] ^{18}O-Labeled **5a*** was prepared from *N*-methyl-*N*-[^{18}O]benzoylglycine, obtained by the Schotten-Baumann reaction of *N*-methylglycine with [^{18}O]benzoyl chloride.



Scheme 10. Hydrolysis and methanolysis reaction products of 5



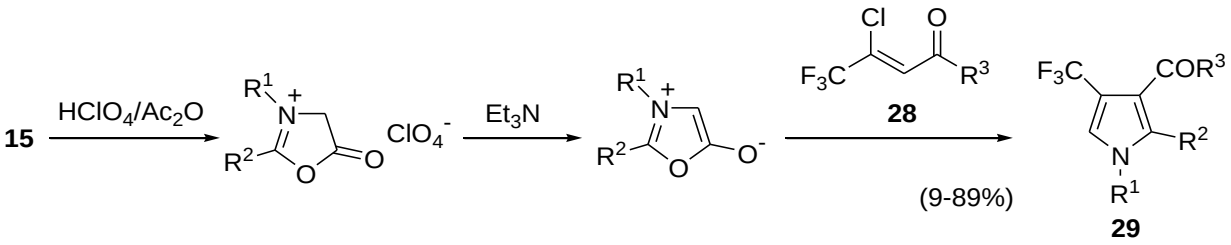
Scheme 11. Hydrolysis of ^{18}O-labeled 5a* and 5a

Thus, hydrolysis of **5a*** (^{18}O content: 94%) with H_2O gave trifluoromethyl ketone hydrate **26a*** (^{18}O content: 93%). In the hydrolysis of **5a** with $H_2{}^{18}O$, ^{18}O was not incorporated into the amide carbonyl of product **26a**. Therefore, it is evident that the reaction proceeds through regioselective attack of H_2O on the C-5 position of **5a** (pathway a) and not the C-2 position (pathway b), as described by Singh *et al*.[21] These data are consistent with an MO study indicating that *N*-nucleophiles attack at the C-2 position and *O*-nucleophiles attack at the C-5 position on the basis of the HSAB theory.[38]

3-2. Trifluoromethyl-substituted pyrroles

3-2-1. Reaction with enamines

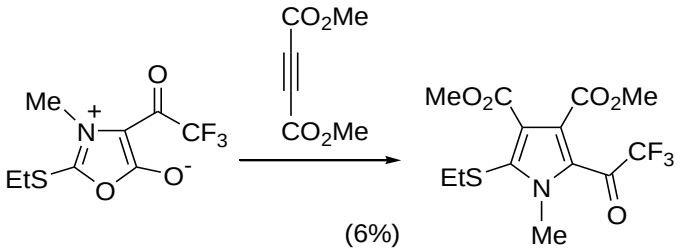
In pioneering work on the 1,3-dipolar cycloaddition of münchnones, Huisgen and co-workers reported that the reaction of münchnones with acetylenes substituted with one or two electron-withdrawing groups can be used to synthesize a great variety of substituted pyrroles (Scheme 1, eq. 2).[39] In 1991, the münchnones cycloaddition reaction with trifluoromethylated dipolarophiles **28** to afford β-trifluoromethylpyrrroles **29** was reported (Scheme 12).[40]



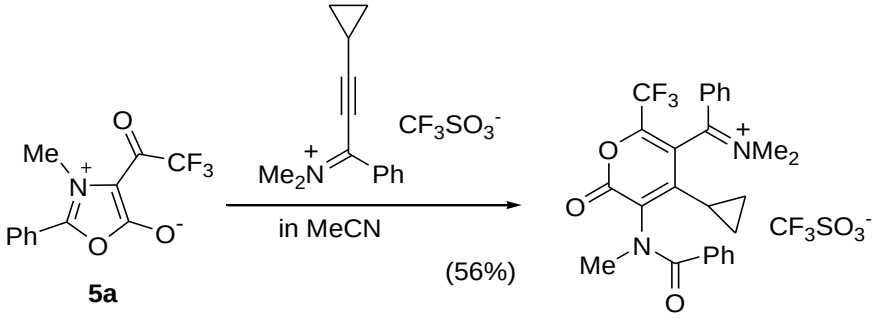
R^1 = Me, Ph; R^2 = Me, Ph; R^3 = Ph, OC_4H_9

Scheme 12. 1,3-Dipolar cycloaddition of münchnones and trifluoromethylated dipolarophiles 28

However, because of the strongly electron-withdrawing trifluoroacetyl group, 4-TFMK-münchnones **5** do not easily undergo 1,3-dipolar cycloaddition reactions with double- or triple-bonded electron-poor dipolarophiles. In fact, 2-ethylthio-3-methyl-4-trifluoroacetyl-1,3-oxazolium-5-olates with dimethyl acetylenedicarboxylate at 120 °C underwent 1,3-dipolar cycloaddition followed by extrusion of CO_2 to afford a pyrrole with a poor yield of 6% (Scheme 13).[41] In addition, 3-methyl-2-phenyl-4-trifluoroacetyl-1,3-oxazolium-5-olate (**5a**) did not undergo 1,3-dipolar cycloaddition reactions with acetylenic iminium salts; instead, Michael addition and a six-electron electrocyclic ring closure yielded pyranone derivatives (Scheme 14).[42]

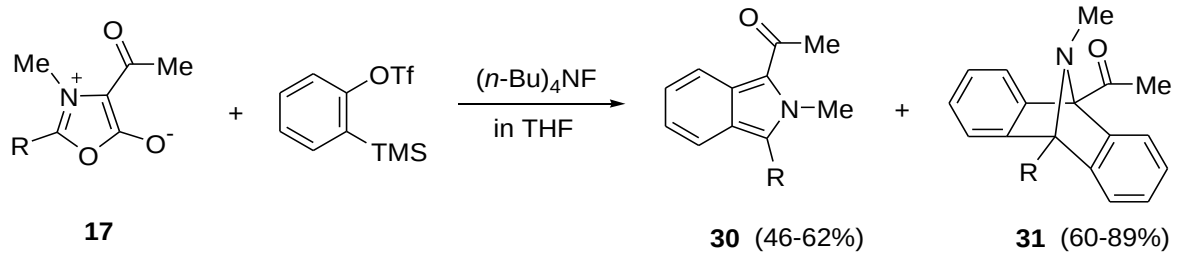


Scheme 13. 1,3-Dipolar cycloaddition of 4-TFMK-münchnones and dimethyl acetylene dicarboxylate



Scheme 14. Cycloaddition of 5a and acetylenic iminium salts

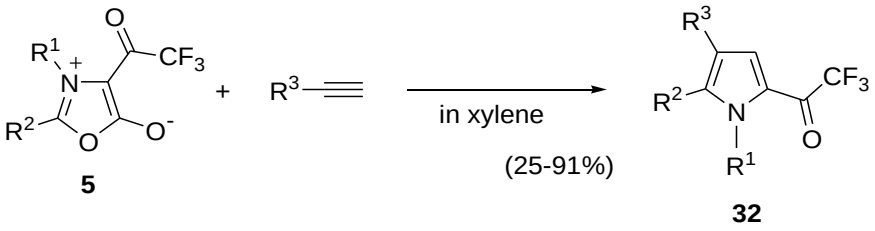
Characteristically, arynes do not react with **5a**, whereas 4-acetylmünchnones **17** do undergo a cycloaddition because the acetyl group is less electron withdrawing than the trifluoroacetyl group (Scheme 15). The reaction expands aryne dipolar cycloaddition with **17** to afford mixtures of isoindoles **30** and 9,10-dihydro-9,10-epiminoanthracenes **31**, which arise from a second cycloaddition of the aryne and **30**.[19]



R = Ph, 3-MeC_6H_5, 4-MeC_6H_5, 4-ClC_6H_5

Scheme 15. Aryne cycloaddition of 4-acetylmünchnones

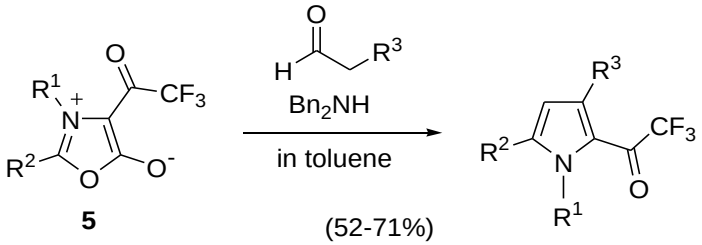
In a relatively successful example, Harrity *et al*. reported that the cycloaddition of 4-TFMK-münchnones **5** with aryl-substituted alkynes gave a good yield of 2-trifluoroacetylpyrroles **32**, whereas the reaction with alkyl-substituted alkynes proved to be much less reactive (Scheme 16).[20]



5 **32**

R^1 = Me, Bn, Ph; R^2 = Me, Ph; R^3 = C_6H_{13}, cyclopropyl, Ph

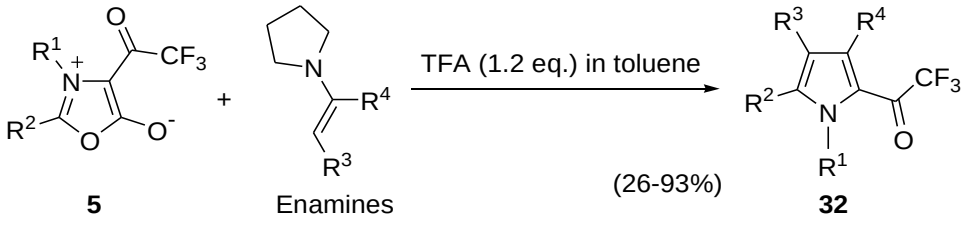
Scheme 16. Cyclization of 5 and alkynes



5 **32**

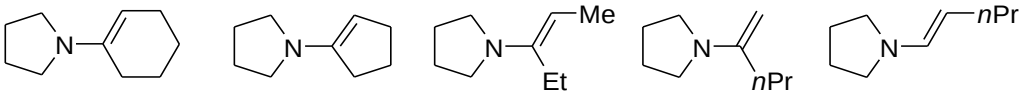
R^1 = Me; R^2 = Me, Ph; R^3 = *n*-Bu, Bn, 3-pyridylmethyl. Ph, 4-ClC_6H_4

Scheme 17. Cyclization of 5 and *in situ* generated terminal enamines



5 **32**

Enamines:

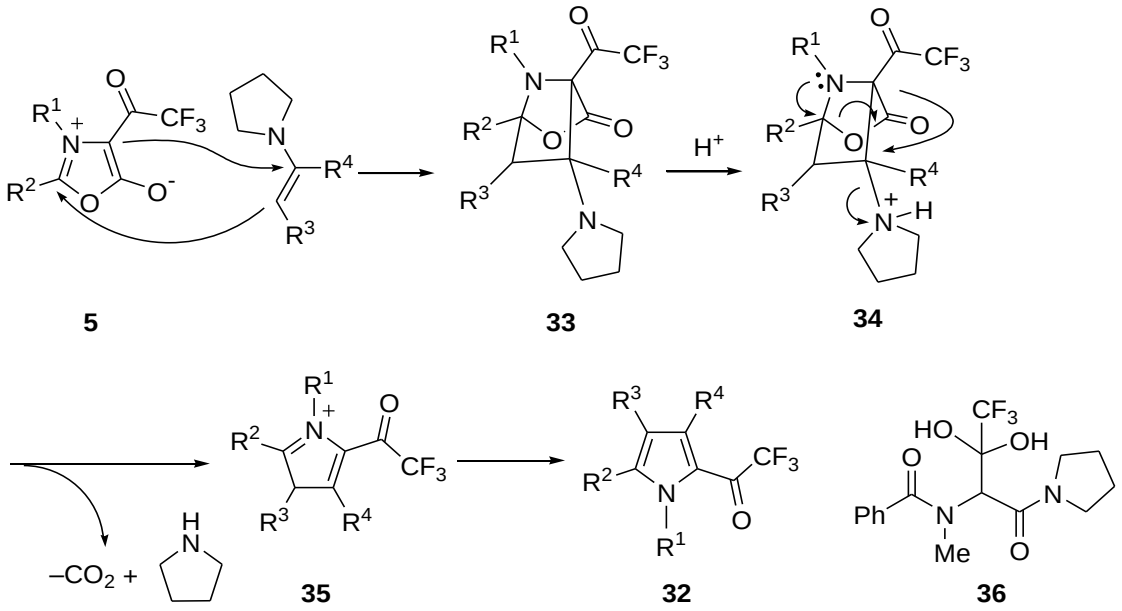


R^1 = Me, Bn, Ph; R^2 = Me, Ph

Scheme 18. Cyclization of 5 and enamines

The cycloaddition reaction of **5** with enamines was successful. Harrity *et al*. reported a limited number of reactions between **5** and terminal enamines (Scheme 17).[43] In addition, the same reaction was applied to a variety of enamines; it represents a general entry to substituted 2-trifluoroacetylpyrroles **32**, proving the usefulness of 1,3-dipolar cycloadditions of **5** with enamines (Scheme 18).[44] During the reaction, addition of trifluoroacetic acid (TFA) increases the yields of the cycloaddition products. Enhanced reactivity and high regioselectivity are also observed in the cycloaddition of **5** with enamines, and the regioselective outcome has been verified through the syntheses of 3,4-disubstituted pyrroles **32**. Considering the variety

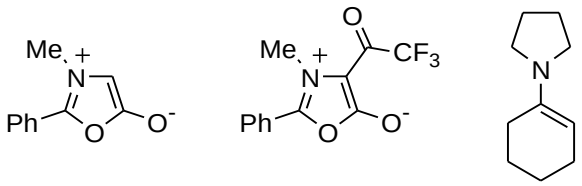
of enamines that react with **5**, this approach can in principle provide access to a range of 2-trifluoroacetylpyrroles **32**.



Scheme 19. Mechanism of the reaction of 5 and enamines

The reaction involves a typical 1,3-dipolar cycloaddition to give bicyclic adduct **33** (Scheme 19). Intermediate **33** is protonated by TFA to produce intermediate **34**, which releases CO_2 and pyrrolidine to give the pyrrole **32** *via* intermediate **35**. In the reaction, the role of TFA may be to protonate intermediate **33** and facilitate the elimination of pyrrolidine. Another role of TFA could be to trap pyrrolidine produced from the enamines, avoiding the formation of the side products such as **36** (Scheme 19).

Table 2. LUMO and HOMO energies (eV units)[a] of münchnones and dipolarophiles



3a **5a** **37**

	3a	**5a**	**37**	Methyl propiolate
LUMO	– 1.905	– 2.694	0	– 1.823
HOMO	– 5.252	– 6.368	– 4.735	– 8.028

[a] DFT calculations at the B3LYP / 6-31+G (d, p) level of theory.

In order to assess the effects of the trifluoroacetyl group at the 4-position in **5**, DFT calculations for **5a** (R^1 = Me, R^2 = Ph) and 4-unsubstituted münchnone **3a** (R^1 = Me, R^2 = Ph) were carried out according to the B3LYP/6-31+G (d, p) method.[45] The results are summarized in Table 2 and clearly show the differences in the LUMO and HOMO levels. Calculations were also performed for 1,3-dipolarophiles such as enamine **37** and methyl propiolate. Münchnone **3a**, bearing a hydrogen atom at the 4-position, has relatively higher energy levels for the LUMO and HOMO. Thus, the typical 1,3-dipolar cycloaddition of münchnones with electron-poor dipolarophiles is considered to be a HOMO-$_{\text{dipole}}$ and LUMO-$_{\text{dipolarophile}}$ controlled reaction.[46]

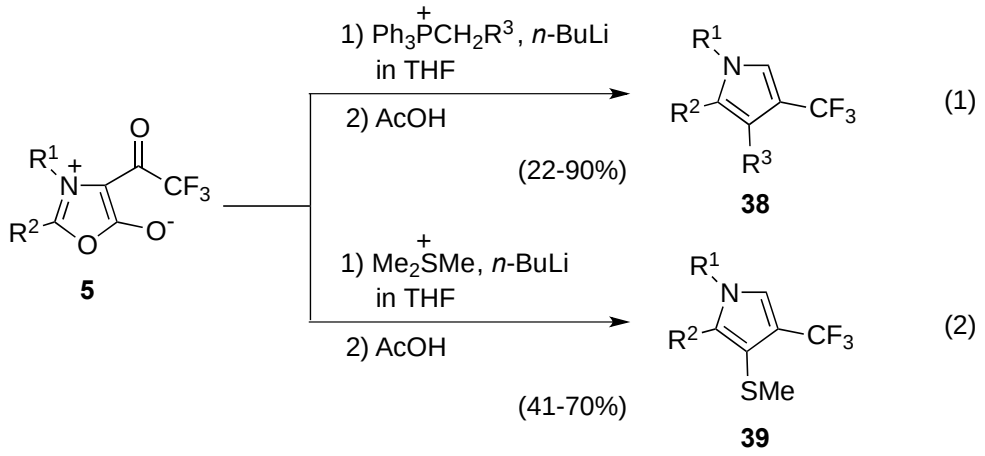
By contrast, 4-TFMK-münchnone **5a** has relatively low energy levels for the LUMO and HOMO. Therefore, the introduction of an acyl function at the 4-position in münchnones usually suppresses cycloaddition with electron-poor dipolarophiles. Conversely, 1,3-dipolar cycloaddition of electron-rich olefins, such as enamines, is expected to be a LUMO-$_{\text{dipole}}$ and HOMO-$_{\text{dipolarophile}}$ controlled reaction.[47,48] The energy values for the HOMOs/LUMOs of **5a** and enamine **37** lead us to believe that the $\text{LUMO}_{\text{dipole}}$–$\text{HOMO}_{\text{dipolarophile}}$ interaction is prevalent (ΔE = –2.041 eV versus –6.368 eV for the opposite HOMO–LUMO pair). Thus, the 1,3-dipolar cycloaddition should involve the LUMO of **5** (1,3-dipole) interacting with the HOMO of the enamine (dipolarophile). Therefore, the regioselectivity arises from a combination of two kinds of attractive interactions operating in the transition state and the reaction can proceed through concerted asynchronous mechanisms which were reported in the cycloaddition of nitroethane and electron-rich alkenes.[49]

3-2-2. Reaction with P-ylides or S-ylides

The reaction of P-ylides with **5** gives 1,2-disubstituted and 1,2,3-trisubstituted 4-trifluoromethylpyrroles **38** (Scheme 20, eq. 1).[50] The reaction begins with P-ylides attacking at the C-2 position of **5** (Scheme 21). In order for this reaction to be successful, it is necessary to add acetic acid or hexafluoro-2-propanol and apply heat after the reaction with ylide. The reason for this is believed to be to facilitate elimination of $Ph_3P{=}O$ after the formation of intermediate **40** in the reaction.

Similarly, the reaction of S-ylides with **5** proceeds through nucleophilic addition at the C-2 position to form multisubstituted pyrroles **39** bearing both an alkyl(aryl)thio and a trifluoromethyl group at the 3- and 4-positions (Scheme 20, eq. 2).[51] In the reaction, side product **41** is also obtained (Scheme 22). In general, 2- or 5-substituted pyrroles are easily synthesized by aromatic electrophilic substitution, such as trifluoromethylation, whereas a special strategy is necessary to obtain 3- or 4-substituted pyrroles.[52] Therefore, these reactions are valuable as synthetic methods for pyrroles with trifluoromethyl groups introduced at the 3- or 4-positions. Together, these reactions provide an effective approach to construct

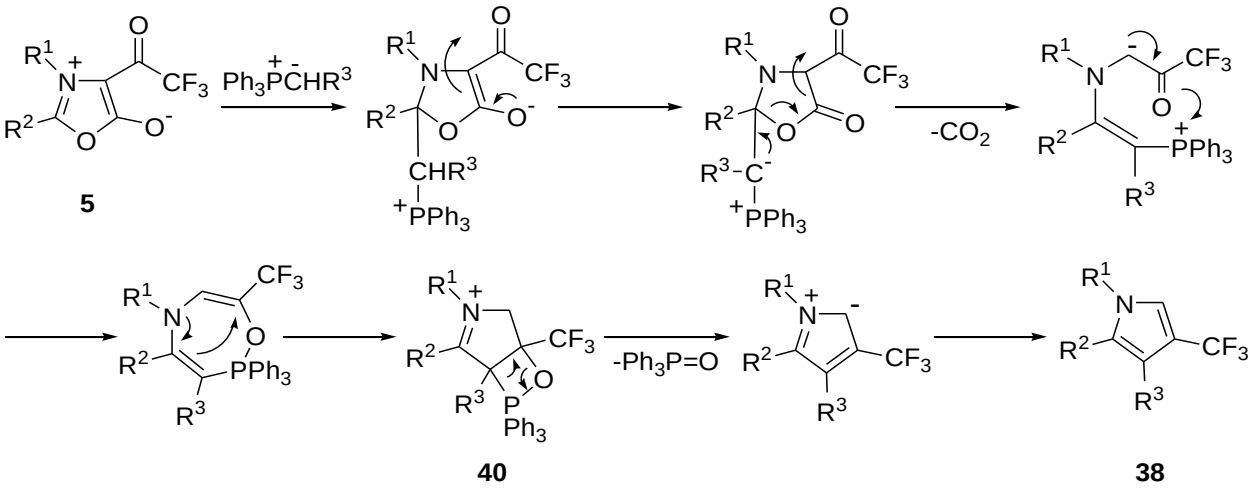
pyrroles, in which the substitution at any position on the product can be modified by changes to the P- and S-ylides or münchnones **5**.



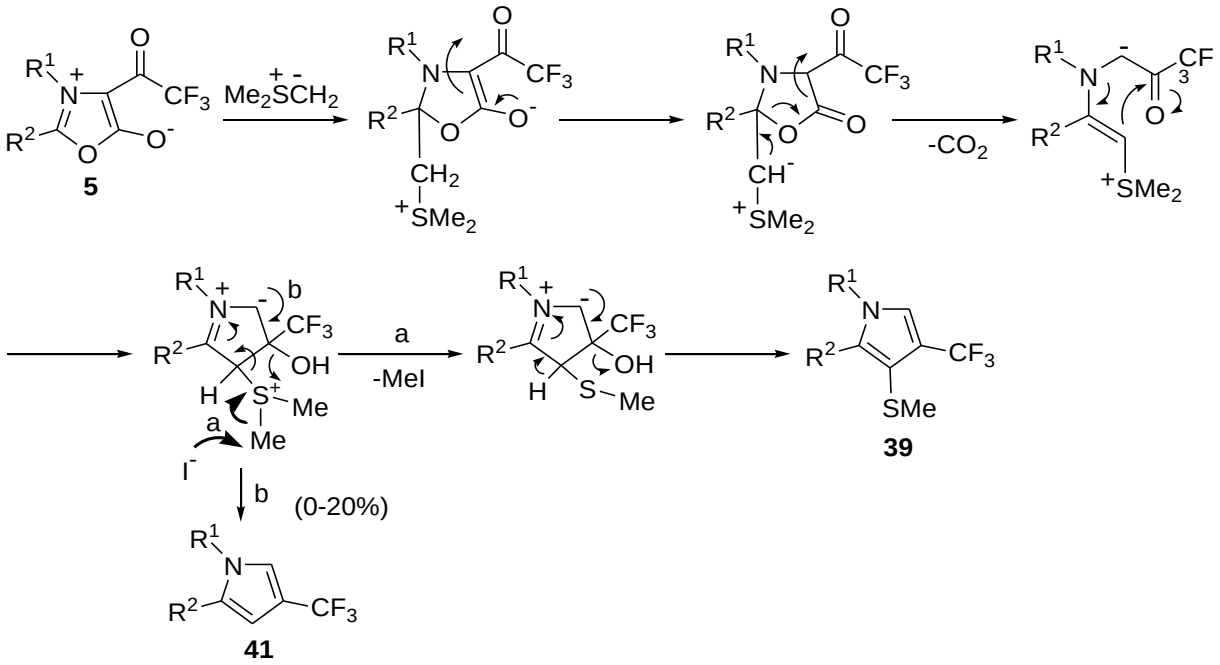
R^1 = Me, Bn, Ph; R^2 = Me, *t*-Bu, Ph, 4-$MeOC_6H_5$; R^3 = H, Me, Pr, C_8H_{17}, OMe (eq. 1)

R^1 = Me, Bn, Ph; R^2 = Me, Ph, 4-$MeOC_6H_4$ (eq. 2)

Scheme 20. Reactions of 5 with P-ylides or S-ylides



Scheme 21. Mechanism for the formation of 4-trifluoromethylimidazoles 38

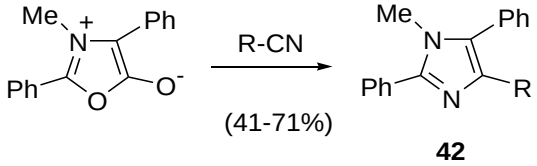


Scheme 22. Mechanism for the formation of 4-trifluoromethylimidazoles 40

3-3. Trifluoromethyl-substituted imidazoles

3-3-1. Reaction with amidines

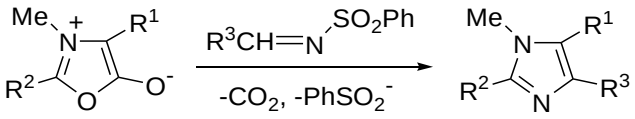
Studies by the Huisgen group demonstrated the preparation of imidazoles by treating münchnones with electron-deficient nitriles (Scheme 23).[53] This method involves a 1,3-dipolar cycloaddition reaction of münchnones and affords imidazoles **42** containing electron-withdrawing groups in moderate yields.



R = CO_2Et, COPh, OPh

Scheme 23. 1,3-Dipolar cycloaddition of münchnones with electron-deficient nitriles

Construction of the imidazole scaffold can also be performed by treating münchnones with *N*-phenylsulfonyl imines (Scheme 24).[53,54] The procedure involves a 1,3-dipolar cycloaddition reaction and the phenylsulfonyl moiety of the imines is a good leaving group. The Arndtsen group also reported that *in situ* generated montréalones **13** reacted with *N*-nosyl imines to give imidazoles.[55] In addition, a palladium-catalyzed synthesis of 2-arylimidazoles by the 1,3-dipolar cycloaddition of *in situ* generated münchnones with *N*-tosyl imines was developed by Arndtsen *et al*.[56]



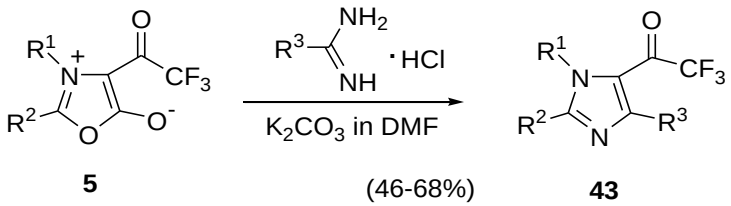
(20-65%)

R^1 = Me, Ph; R^2 = Me, Ph; R^3 = H, Ph, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$

Scheme 24. 1,3-Dipolar cycloaddition of münchnones with *N*-phenylsulfonyl imines

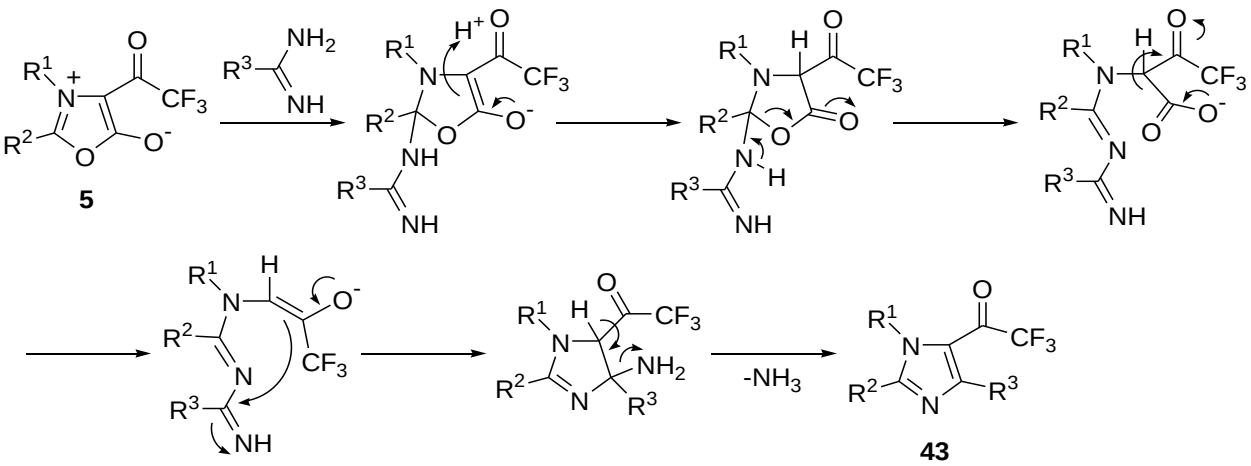
The solid-supported synthesis of imidazoles by similar reactions with münchnone generation and cyclization with *N*-tosyl imines has also been reported.[57]

4-TFMK-münchnones **5** react with amidines to afford trisubstituted 5-trifluoroacetylimidazoles **43** in moderate yields (Scheme 25).[23] The proposed mechanism, in which the amidines attack at the C-2 position of **5**, is illustrated in Scheme 26.



R^1 = Me, Ph; R^2 = Me, *t*-Bu, Ph

Scheme 25. Reaction of 5 with amidines

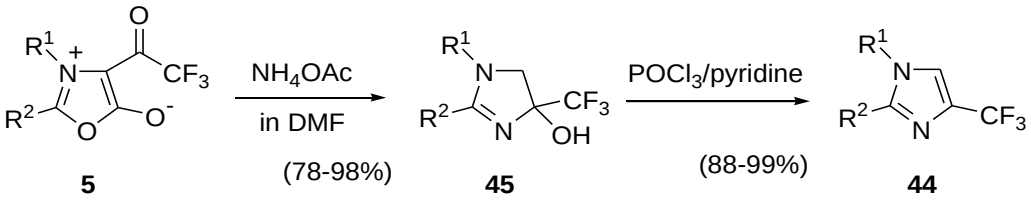


Scheme 26. Mechanism for the formation of 5-trifluoroacetylimidazoles 43

Hamper and co-workers employed a solid-phase protocol for the generation of a library of 200 5-trifluoroacetylimidazoles based on the reaction of **5** with amidines.[58] Trifluoroacetylation of 1-alkyl-substituted imidazoles gave 2-trifluoroacetylimidazoles in good yields.[59] Therefore, 5-trifluoroacetylimidazoles **43** seem less likely to be synthesized by other methods.

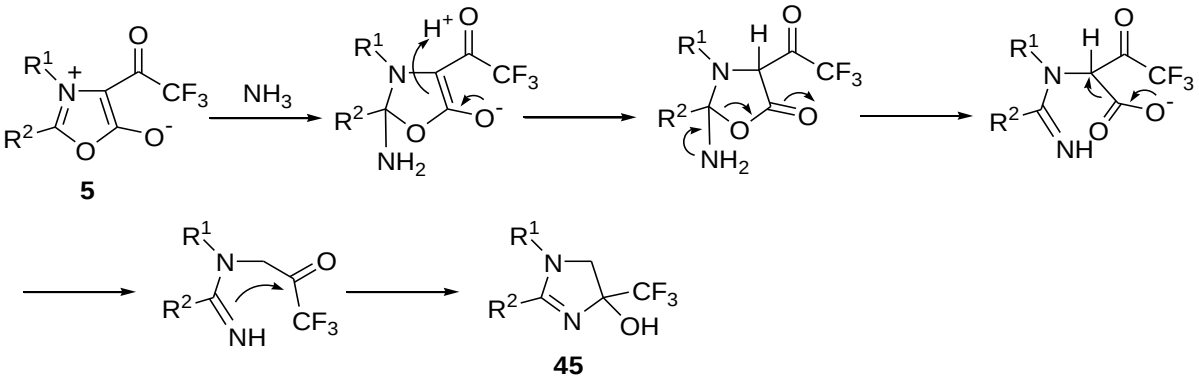
3-3-2. Reaction with ammonia

4-Trifluoromethylimidazoles **44** are accessible *via* the reaction of **5** with ammonium acetate in DMF followed by dehydration in two steps (Scheme 27).[37] This aminolysis of **5** with ammonia proceeds by initial attack at the C-2 position of **5**, followed by ring opening, decarboxylation, and cyclization to give 4,5-dihydroimidazoles **45** (Scheme 28). Dehydration of product **45** by the reaction of phosphorus oxychloride and pyridine gives 5-unsubstituted 4-trifluoromethylimidazoles **44** in high yields. This reaction is also applicable to the syntheses of 4-pentafluoroethyl and 4-heptafluoropropylimidazoles.[37]



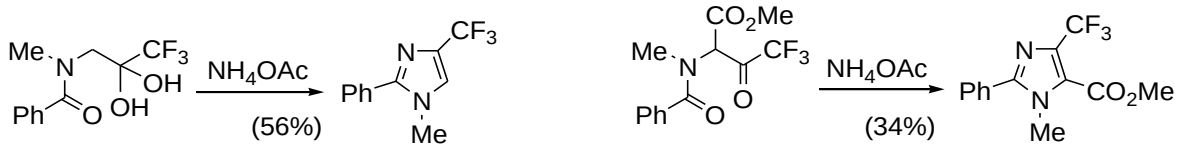
R^1 = Me, Bn, Ph; R^2 = Me, *t*-Bu, Bn, Ph

Scheme 27. Reaction of 5 with ammonium acetate



Scheme 28. 4-Trifluoromethylimidazoles 44 and 4-trifluoromethyldihydroimidazoles 45 from 5

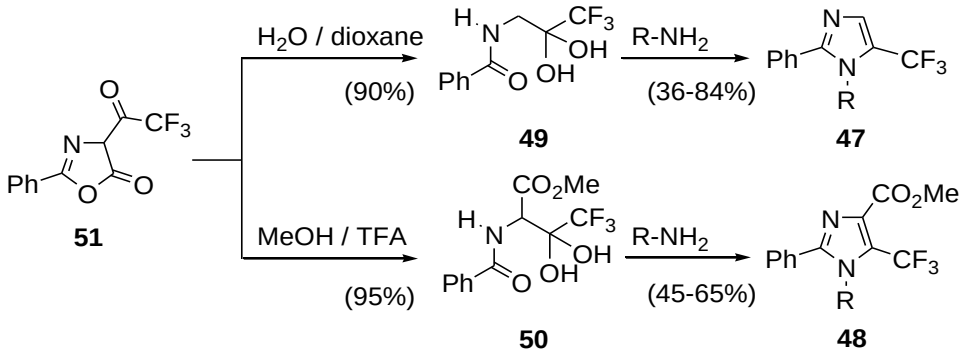
Hydrolysis of **5a** affords trifluoromethyl ketone hydrate **26** in 83% yield (Scheme 10, eq. 1).[60] When the methanolysis of **5a** is performed in MeOH in the presence of TFA, the product α-trifluoroacetyl-*N*-acylglycine ester **27** is obtained in 91% yield (Scheme 10, eq. 2). The reactions of **26** and **27** with ammonium acetate afford the corresponding 4-trifluoromethylimidazoles **45** and **46**, respectively, in moderate yields (Scheme 29).[60]



26 **45** **27** **46**

Scheme 29. Preparation of 4-trifluoromethylimidazoles 45 and 46

The isomeric 5-trifluoromethylimidazoles **47** and **48** were prepared by the reactions of **49** and **50**, respectively, with ammonia or primary amines in moderate yields; compounds **49** and **50** were obtained by the reactions of 4-trifluoroacetylazlactone **51** with H_2O or MeOH, respectively (Scheme 30).[60] Compound **51** is structurally related to **5** and can be prepared at a high yield by the reaction of *N*-benzoylglycine and TFAA.[60] However, its synthetic potential has not been fully explored as a CF_3 synthon.[60] A close look at the structure of **27** and **50** reveals that these compounds contain a carbon substituted with three different reactive functional groups, such as trifluoromethyl ketones, esters, and amides. In 2012, Moody and co-workers reported that ethyl esters of type **50** could be obtained through the rhodium-catalyzed reaction of ethyl 2-diazo-4,4,4-trifluoro-3-oxobutanoate and benzamides in low yields (32-43%).[61] Several examples of subsequent cyclizations have afforded CF_3-substituted oxazoles, imidazoles, and thiazoles.[60]



51 **49** **47** **50** **48**

R = H, Me, C_6H_{13}, Bn

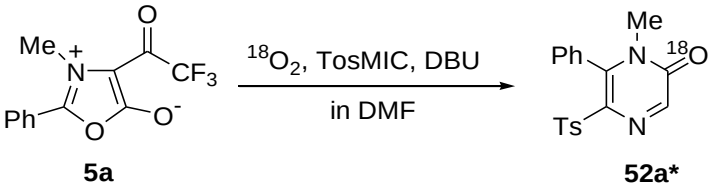
Scheme 30. Preparation of 5-trifluoromethylimidazoles 47 and 48

3-4. 2(1*H*)-Pyrazinones and imidazo[1,5-*a*]pyrazin-8(7*H*)-ones

3-4-1. Reaction with TosMIC or $EtOCOCH_2NC$

The reaction of **5** with *p*-toluenesulfonylmethyl isocyanate (TosMIC) in the presence of a base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) affords 2(1*H*)-pyrazinones **52** in moderate yields.[26,62] The origin of the C-2 carbonyl oxygen atom in the product **52a*** (R^1 = Me, R^2 = Ph) was shown to be molecular oxygen by ^{18}O-labeling experiments (Scheme 31). This novel ring transformation reaction

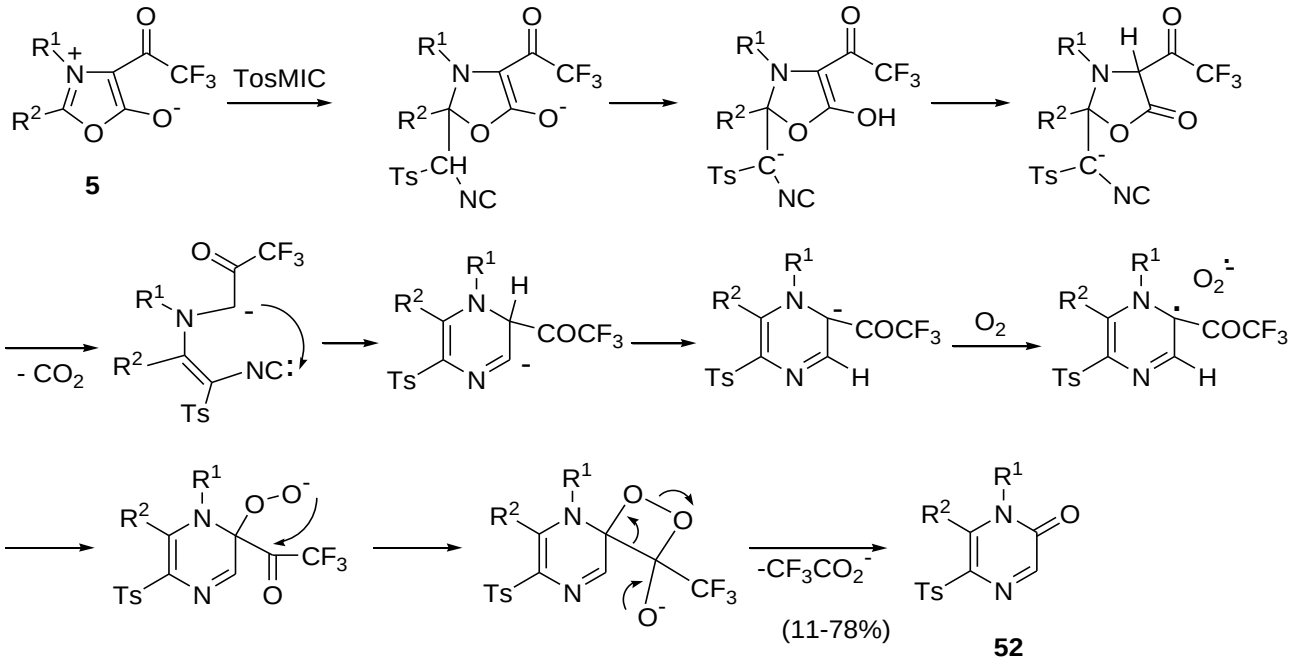
proceeds *via* an initial attack of TosMIC anions on the C-2 position of **5**, opening of the oxazole ring, subsequent cyclization, and autoxidation, which includes oxygenation, cyclization of the resulting peroxy anion, and oxidative cleavage (Scheme 32).



5a **52a***

Scheme 31. Formation of 2(1*H*)-pyrazinones 52a* from 5a

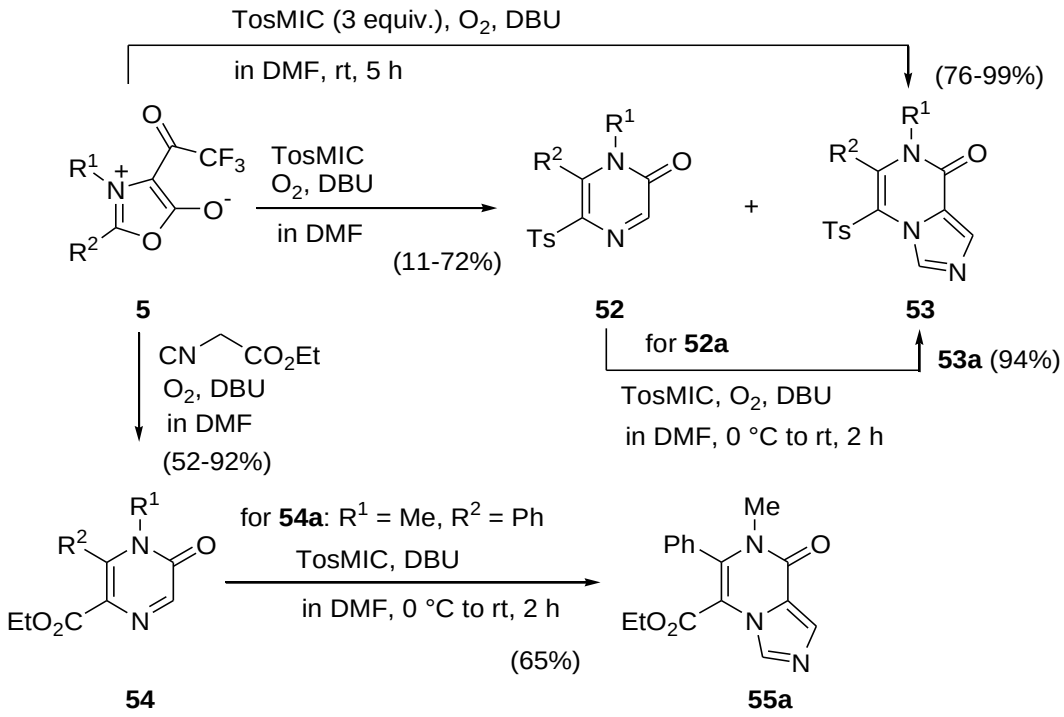
The reaction with TosMIC gives imidazo[1,5-*a*]pyrazin-8(7*H*)-one derivatives **53** as side products. The same ring transformation has been achieved to give **54** by the reaction of **5** with ethyl isocyanoacetate ($EtOCOCH_2NC$), using the same conditions for the reaction with TosMIC (Scheme 33). However, the reaction with $EtOCOCH_2NC$ does not give the side product. In separate experiments, the reaction of **52a** (R^1 = Me, R^2 = Ph) with TosMIC affords **53** in a high yield. The same reaction of **54** with TosMIC also yields imidazo[1,5-*a*]pyrazin-8(7*H*)-one derivative **55a** (R^1 = Me, R^2 = Ph). The C-3 positions of **52** and **54** are electrophilically reactive, being part of an imine system.[63] However, the reaction of **52** or **54** with $EtOCOCH_2NC$ fails to give the product under comparable reaction conditions.



5 **52**

R^1 = Me, Bn, Ph, 4-$MeOC_6H_4$; R^2 = Me, *t*-Bu, Ph, 4-BrC_6H_4, 4-$MeOC_6H_4$

Scheme 32. Mechanism for the formation of 2(1*H*)-pyrazinones 52

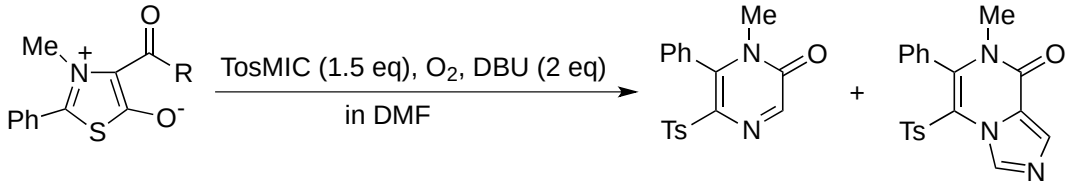


R^1 = Me, Bn, 4-MeOBn, Ph; R^2 = Me, *t*-Bu, Ph, 4-BrC_6H_4, 4-MeOC_6H_4, 4-$NO_2C_6H_4$

Scheme 33. Reaction of 5 with TosMIC or ethyl isocyanoacetate

The imidazo[1,5-*a*]pyrazin-8(7*H*)-one derivatives **53** are obtained in high yields in one step by the reaction of **5** with TosMIC when three molar equivalents of the reagent are used (Scheme 33).[64]

Table 3. Formation of 2(1*H*)-pyrazinone 52a from 4-acyl-1,3-thiazolium-5-olates 18-20[a]



Entry	Compd	R	Conditions	Products (Yield, %)[b]	
				52a	**53a**
1	**18**	CF_3	0 °C, 2 h	68	2
2	**19**	Me	0 °C, 12 h	10	11
3	**20**	H	0 °C, 12 h	13	I 5

[a]Reactions were carried out using **18**-**20 (**0.50 mmol), TosMIC (0.75 mmol) and DBU (1.0 mmol) in DMF (3 mL) under an oxygen atmosphere. [b]Isolated yield.

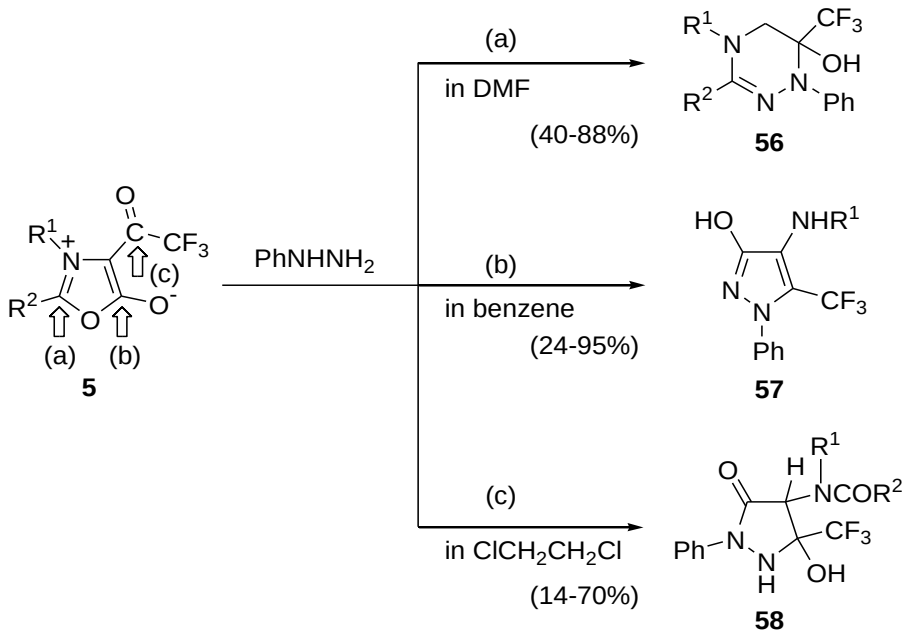
In order to examine the effect of the 4-trifluoroacetyl group in **5**, three acyl derivatives, namely the trifluoroacetyl, acetyl, and formyl derivatives, **18-20**, of 1,3-thiazolium-5-olates have been subjected to

the same reaction conditions with **5** and TosMIC. As shown in Table 3, the trifluoroacetyl derivative **18** gives the product **52a** in higher yields than the acetyl and formyl derivatives **19** and **20**.

3-5. Reactions with *bis*-nucleophiles

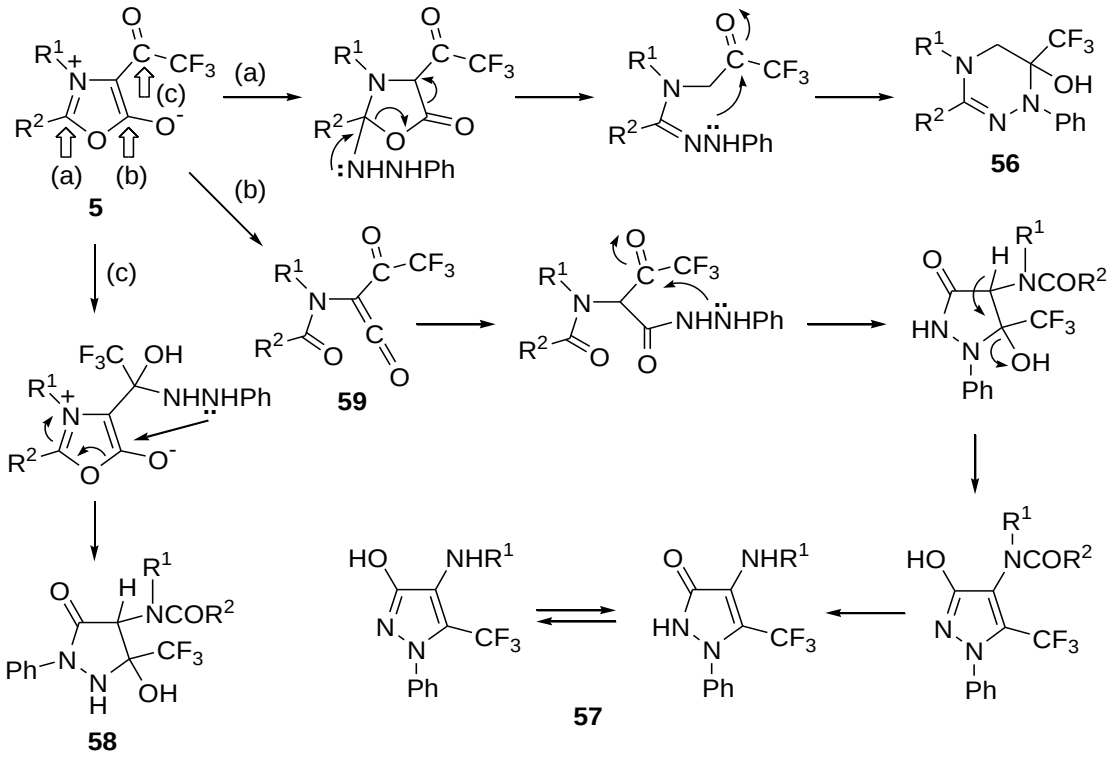
3-5-1. Reaction with $PhNHNH_2$

The reaction of **5** with phenylhydrazine produces three different products **56**-**58**, depending on the nature of the solvent and the reaction temperature (Scheme 34).[65] Thus, in polar DMF, 1,2,4-triazines **56** are obtained by a C-2 attack on the mesoionic form of **5** (Scheme 35, pathway a). However, in refluxing benzene solution, pyrazoles **57** are produced by a C-5 attack of the ring-opened ketene **59** (Scheme 35, pathway b). Finally, in 1,2-dichloroethane, pyrazolones **58** are obtained from an attack on the trifluoromethyl ketone group of **5** (Scheme 35, pathway c). Based on the model, the three modes of regioselective attack by phenylhydrazine are found to provide three different products. However, the reactions of a DMF solution of **5** with other hydrazine derivatives, such as hydrazine hydrate, methylhydrazine, hydrazine carbamate, or tosylhydrazine, produces 1,2,4-triazines in moderate yields. Compound **57a** (R^1 = Me) treated with benzoyl chloride in the presence of pyridine gives 5-trifluoromethylpyrazole derivative **60** in 87% yield (Scheme 36, eq. 1). By contrast, isomeric 3-trifluoromethylpyrazole derivative **61** is obtained through dehydration and benzoylation of **58a** (R^1 = Me, R^2 = Ph) by reaction with benzoic anhydride in refluxing benzene solution (Scheme 36, eq. 2).

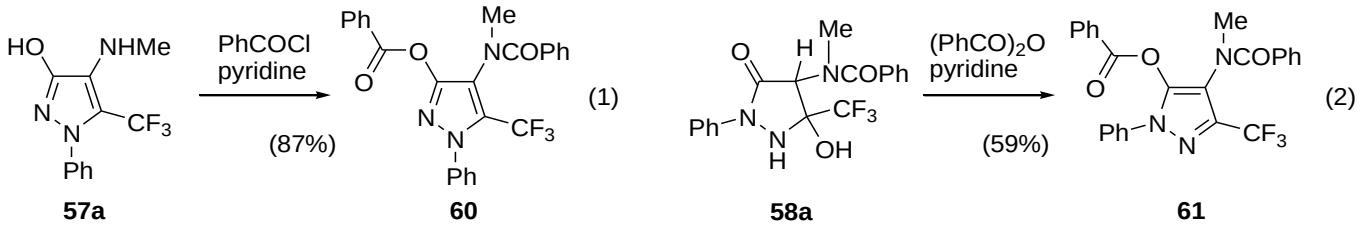


R^1 = Me, Bn, Ph; R^2 = Me, *t*-Bu, Ph, 4-BrC_6H_4, 4-$MeOC_6H_4$

Scheme 34. Reactions of 5 with phenylhydrazine



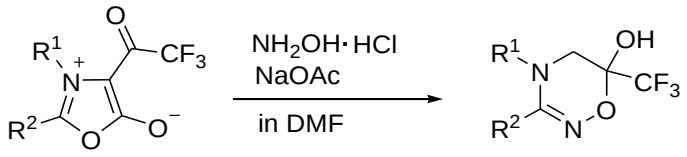
Scheme 35. Mechanism for the formation of products 56-58



Scheme 36. Benzoylation of 57a and 58a to give 5- or 3-trifluoromethylpyrazoles 60 and 61

3-5-2. Reaction with NH_2OH

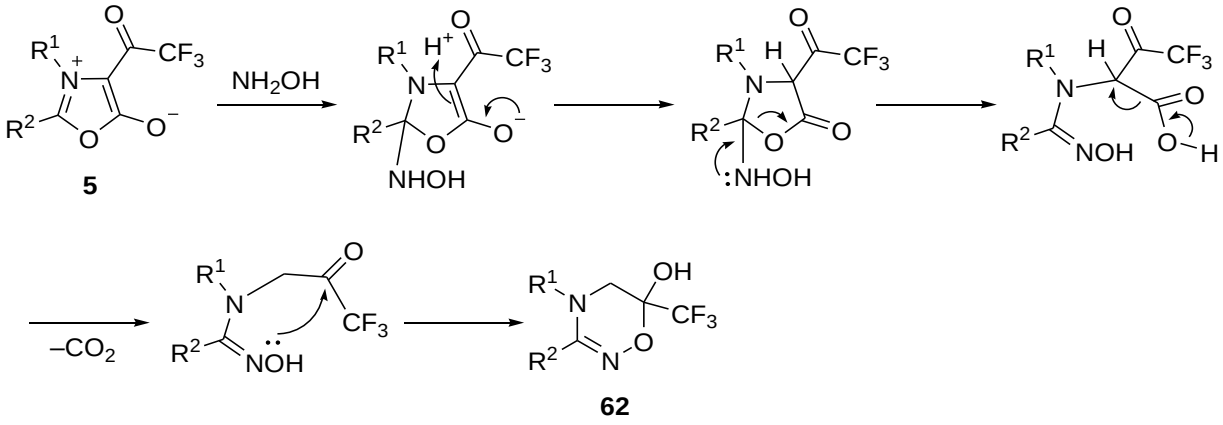
Compounds **5** undergo tandem ring opening and ring closure on addition of hydroxylamine to afford 6-trifluoromethyl-1,2,4-oxadiazin-6-ols **62** in high yields (Scheme 37).[66] In this reaction, initial attack at the C-2 position, ring opening, and extrusion of carbon dioxide are followed by intramolecular cyclization (Scheme 38). The reaction is influenced by the solvent and base. The best result is obtained from the reaction of **5** with hydroxylamine hydrochloride in DMF in the presence of sodium acetate at 80 °C for 3 h. The use of toluene and 1,2-dichloroethane as the solvent diminishes the yield of product. If K_2CO_3 and sodium trifluoroacetate are used as the base, product yields are also reduced.



5 **62**

R^1 = Me, Bn, Ph; R^2 = Me, *t*-Bu, Ph

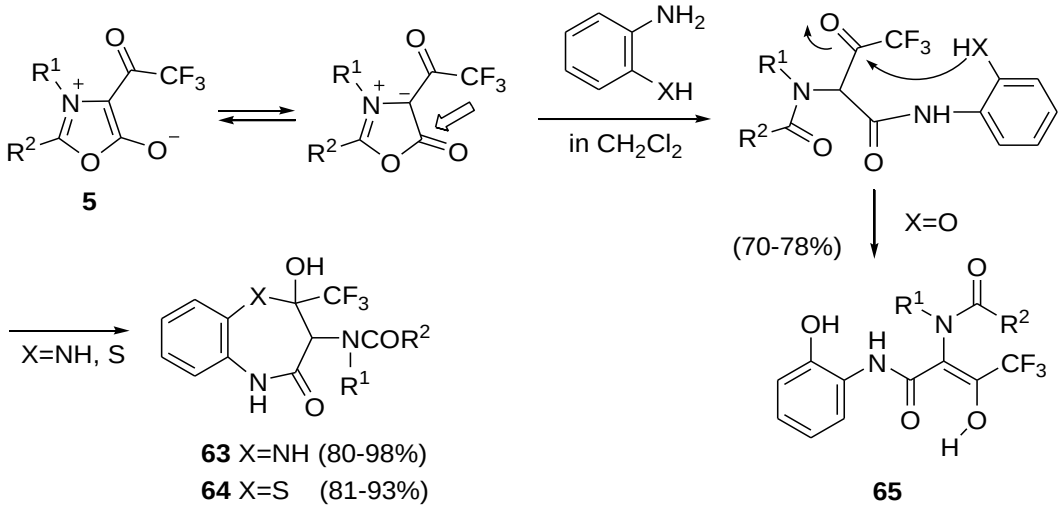
Scheme 37. Reaction of 5 with hydroxylamine



5 **62**

Scheme 38. Mechanism for the formation of 6-trifluoromethyl-1,2,4-oxadiazin-6-ols 62

3-5-3. Reaction with *ortho*-substituted anilines



63 X=NH (80-98%)
64 X=S (81-93%)

65

R^1 = Me, Bn, Ph; R^2 = Me, Ph, 4-$MeOC_6H_4$

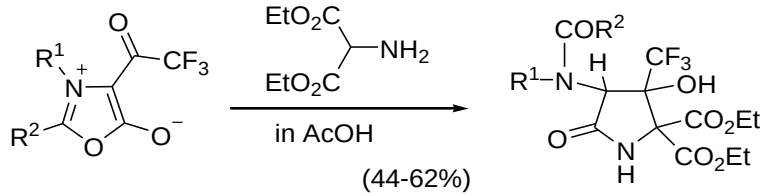
Scheme 39. Reactions of 5 with *o*-phenylenediamine, *o*-aminothiophenol, and *o*-aminophenol

The classical 1,4-binucleophiles *o*-phenylenediamine, *o*-aminothiophenol, and *o*-aminophenol have been introduced into the reaction with 4-TFMK-münchnones **5**.[67] The reactions of **5** and *o*-phenylenediamine

or *o*-aminothiophenol give adducts that undergo further cyclization to 1,5-benzodiazepines **63** or 1,5-benzothiazepines **64**, respectively (Scheme 39). The reaction of **5** and *o*-aminophenol gives adducts **65**, derived from a condensation reaction between the amino group of *o*-aminophenol and the C-5 atom of **5** (Scheme 39).

3-5-4. Reaction with diethyl aminomalonate

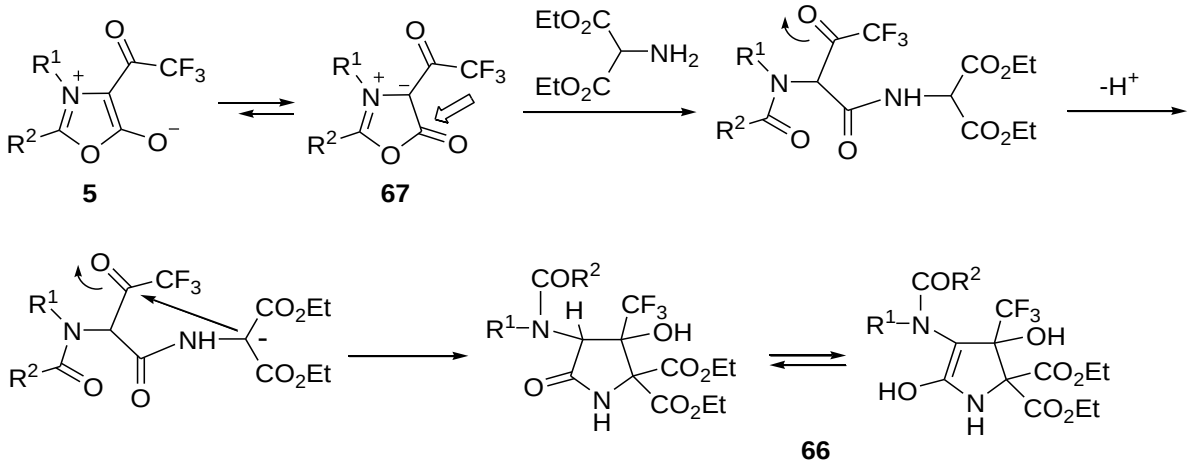
The reaction of 4-TFMK-münchnones **5** with diethyl aminomalonate proceeds in AcOH to give pyrrolidines **66** in moderate yields (Scheme 40).[68] If aprotic solvents such as DMF and benzene are used, no characterized product is obtained. The role of AcOH as the solvent may be to facilitate the formation of keto form **67** in the münchnone (Scheme 41). The reaction of product **66** with Ac_2O in the presence of pyridine affords (2*H*)-pyrrole **68**, which is converted into the highly substituted pyrrole ester **69** by LiOH hydrolysis followed by decarboxylation (Scheme 42). Attempts to condense **5** with ethyl glycinate or *N*-methylglycinate have been unsuccessful as a result of the less acidic methylene group relative to that of amino malonate.



5 **66**

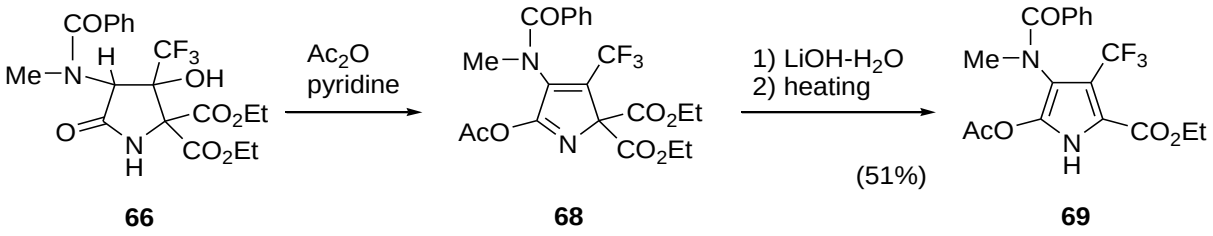
R^1 = Me, Bn, Ph; R^2 = Me, Ph, 4-$MeOC_6H_4$

Scheme 40. Reaction of 5 with diethyl aminomalonate



5 **67** **66**

Scheme 41. Mechanism for the formation of pyrrolidine derivatives 66

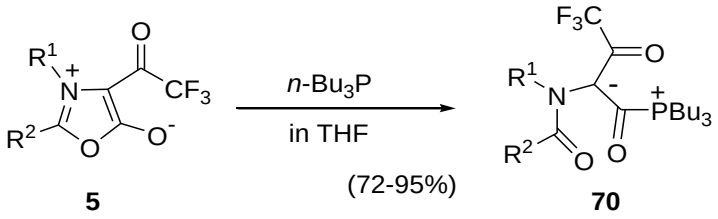


66 **68** **69**

Scheme 42. Conversion of 66 into pyrrole 69

3-6. Reaction with P-nucleophiles

Trialkyl phosphites have been evaluated as phosphorus nucleophiles for the addition reaction of 4-TFMK-münchnones **5**, thereby producing tetravalent phosphorus zwitterions **70** in good yields (Scheme 43).[69] Among the trialkyl or triaryl phosphines tested (including PBu_3, $P(t\text{-}Bu)_3$, PCy_3, and PPh_3), PBu_3 has been found to be the only successful reagent. We speculate that PPh_3, $P(t\text{-}Bu)_3$, and $P(C_6H_{11})_3$ are sterically hindered and not sufficiently nucleophilic toward the mesoionic ring. By contrast, PBu_3 is less sterically hindered and functions as a better nucleophile.[70]



5 **70**

R^1 = Me, Bn, Ph; R^2 = Me, *t*-Bu, Ph, 4-BrC_6H_4

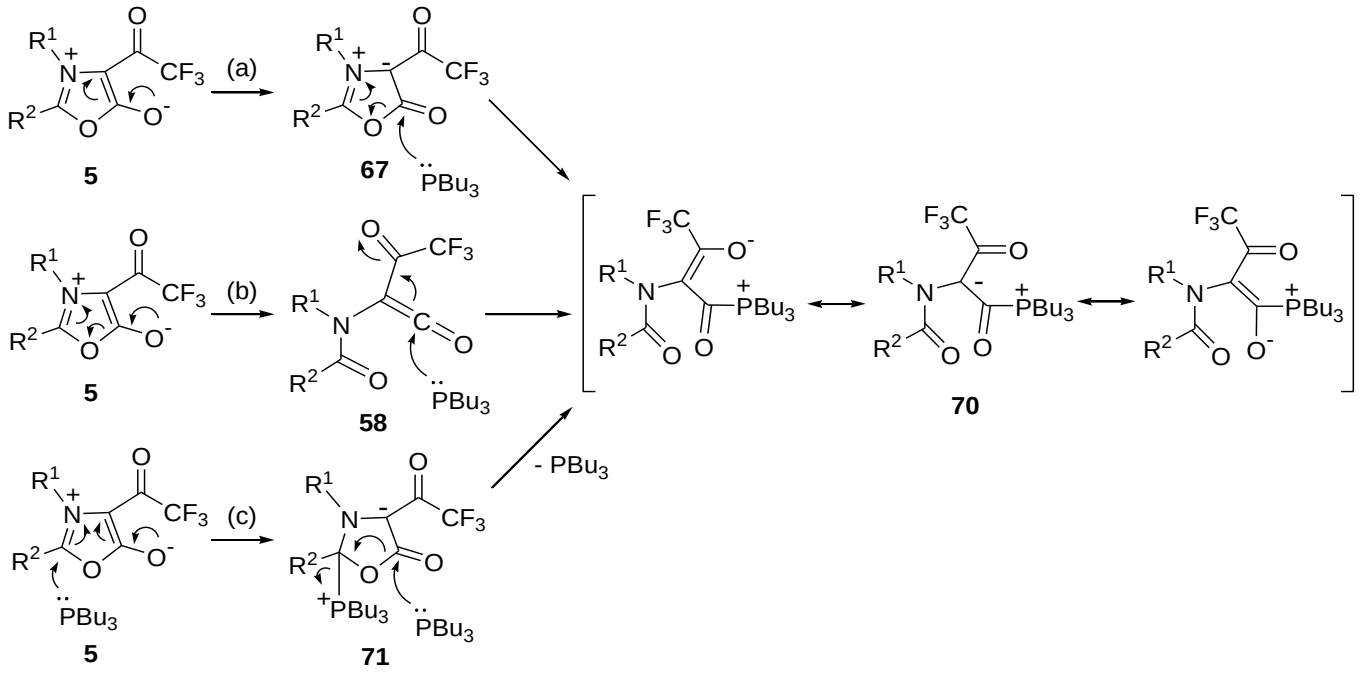
Scheme 43. Reaction of 5 with PBu_3

Triethyl phosphite, $(EtO)_3P$, and diethyl phosphite, $(EtO)_2P(=O)H$, have also been evaluated as P-nucleophiles for addition to **5**. In these reactions, starting material **5** is not recovered and several materials are detected by TLC, none of which has been characterized.

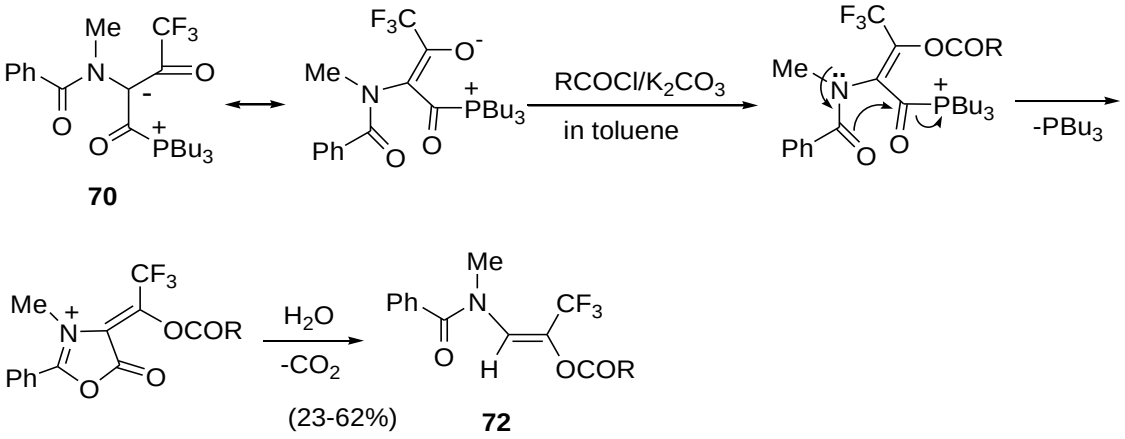
The first example of a novel class of acylphosphonium enolates has become readily available in good yields. We have isolated and characterized some stable acylphosphonium zwitterions that are some of the key intermediates in the PBu_3-catalyzed homodimerization of ketoketenes.[70]

The mechanism has not yet been elucidated in detail; however, the three possibilities are as follows: (1) Bu_3P attacks the tautomeric intermediate **67** to give the resonance-stabilized zwitterionic compounds **70** (Scheme 44, pathway a); (2) Bu_3P attacks ketene intermediate **58** to give **70** because mesoionic **5** is in equilibrium with the ketene in which the ketene carbonyl group is attacked by Bu_3P (Scheme 44, pathway b); (3) Bu_3P acts as a nucleophilic trigger and forms zwitterionic intermediate **71**, which is attacked by a

second Bu_3P to give the ring-opening product **70,** concomitant with regeneration of Bu_3P (Scheme 44, pathway c).



Scheme 44. Mechanism for the formation of acylphosphonium zwitterions 70



R = Me, *i*-Pr, *t*-Bu, Ph

Scheme 45. Formation of enol esters 72 from acylphosphonium zwitterions 70

Acylphosphonium zwitterions **70** have been treated with acyl chloride, and the novel formation of trifluoromethylated enol esters **72** has been observed (Scheme 45).

4. CONCLUSIONS

Our development of one-pot, tandem and domino reactions has greatly enhanced the applicability of 4-TFMK-münchnones **5** as valuable CF_3 synthons for CF_3-substituted heterocycles. The introduction of a trifluoroacetyl group at the 4-position of münchnones enhances the stability of the münchnones and allows them to react with various nucleophiles. In principle, the addition of nucleophiles to **5** can a priori be expected to occur at three different positions (C-2, C-5, or $COCF_3$). In general, *N*-nucleophiles, such as ammonia and amidines, attack at the C-2 position of **5**. Phenylhydrazine demonstrates the remarkable ability to attack at three different positions, depending on the reaction conditions.

The principal advantage of using 4-TFMK-münchnones **5** is the great variety of substituents that are available for R^1 and R^2. This substituent flexibility in **5** will be reflected in the corresponding substitution of the product. Conversely, 4-TFMK-azlactones **51** may be available as synthetic synthons for CF_3-substituted compounds with substitution patterns that cannot be synthesized by 4-TFMK-münchnones.

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