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FLUOROUS THIAZOLIUM SALTS FOR THE INTRAMOLECULAR STETTER REACTION

Osamu Hara,* Atsuko Kume, Michiharu Sugiura, and Isamu Maeba

Faculty of Pharmacy, Meijo University, 150 Yagotoyama Tempaku-ku, Nagoya, Aichi, 468-8503 Japan e-mail : oshara@ccmfs.meijo-u.ac.jp

Abstract – The fluorous thiazolium salt **6** derived from 5-(2-hydroxy-ethyl)-4-methylthiazole was employed for an intramolecular Stetter reaction. The catalytic activity of the fluorous catalyst **6** was similar to that of the standard catalyst **1**. The fluorous catalyst **6** survived multiple reaction cycles.

Since the Stetter reaction was first described in 1973,[1] a number of examples of this reaction using cyanide ion, thiazolium salts, and triazolium salts as a catalyst have been reported including an asymmetric reaction.[2] One unique approach to the Stetter reaction was the use of polymer-supported thiazolium salts catalysts.[3] The polymer catalyst not only was easily separated by simple filtration but also survived 4-6 cycles of the same reaction. Unfortunately, the synthetic utility of the polymer catalysts

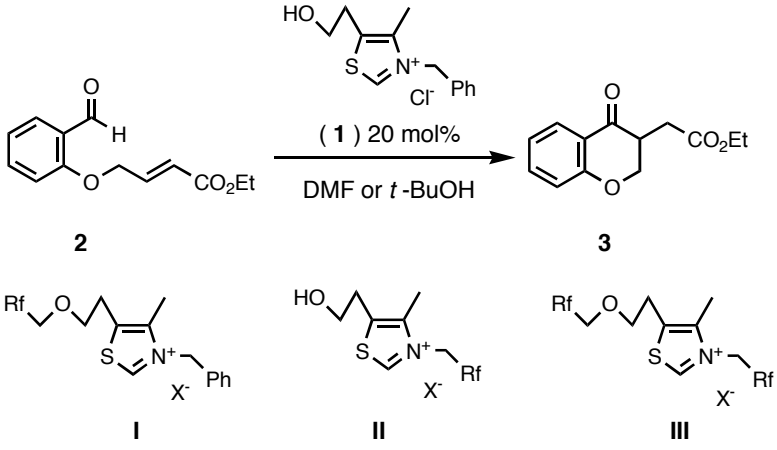


Figure 1. Intramolecular Stetter Reaction and Fluorous Thiazolium Salts

This manuscript is dedicated to Prof. Ryoji Noyori on the occasion of his 70th birthday.

was less than that of a homogenous catalyst. Recently, Curran *et al*. introduced the concept of "fluorous synthesis" as a fundamental strategic alternative to small molecules synthesis and solid phase synthesis.[4] The fluorous synthesis technique features facile purification of fluorous compounds by either extraction with a fluorous solvent or fluorous solid phase extraction.[5] We report herein the synthesis of fluorous thiazolium salts I ~III and its application to an intramolecular Stetter reaction (Figure 1).

An intermediate in thiamine production, 5-(2-hydroxyethyl)-4-methylthiazole, is readily available, and following quarternisation on the thiazole ring and protection of the hydroxyl group with alkyl halide, gives a product that demonstrates catalytic activity in the presence of a base in the intramolecular Stetter reaction. Using the above strategy we succeeded in preparing the corresponding fluorous thiazolium salts (**4** ~ **7**) from 5-(2-hydroxyethyl)-4-methylthiazole. The fluorous catalysts **4** and **5** were readily prepared by the treatment of 5-(2-hydroxyethyl)-4-methylthiazole with perfluorooctylethyl iodide or *p*-(perfluorooctylethyl)benzyl bromide[6] in CH_3CN, respectively. Protection of the hydroxyl group of 5-(2-hydroxyethyl)-4-methylthiazole with *p*-(perfluorooctylethyl)benzyl bromide, followed by quarternisation with benzyl bromide or *p*-(perfluorooctylethyl)benzyl bromide afforded the desired fluorous catalyst **6**[7] and **7**, respectively(Figure 2).

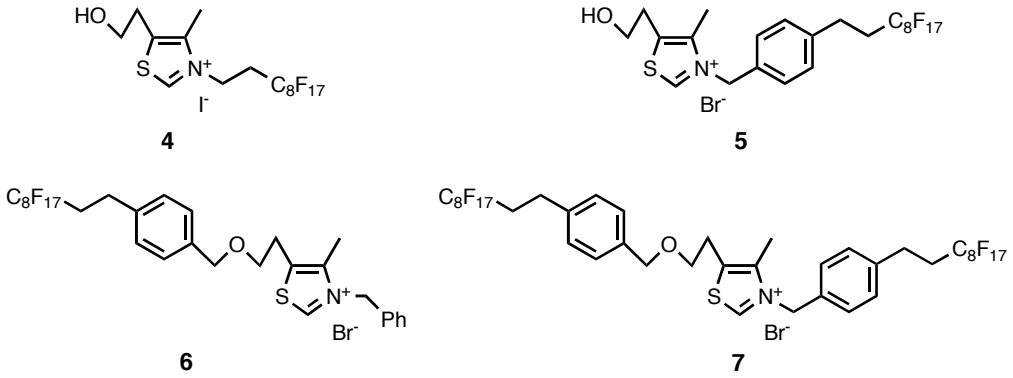
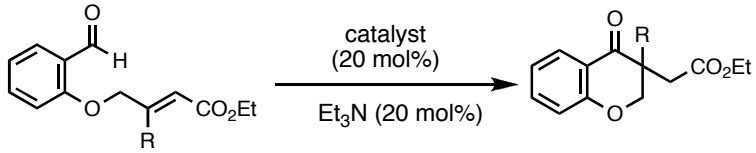


Figure 2. Fluorous Thiazolium Salts

The intramolecular Stetter reaction of salicylaldehyde derivative **2** was investigated using the new fluorous catalysts and the results are summarized in Table 1. The reaction using fluorous catalyst **4** in the presence of Et_3N in DMF required a higher reaction temperature and longer reaction time than that of catalyst **1** to afford the desired product **3** with an unsatisfactory chemical yield (entry 2). Changing the fluorous moiety from an ethyl type to a benzyl type slightly improved reactivity of catalyst (entry 3). Especially, the introduction of the fluorous benzyl moiety to the hydroxyl group, not on the thiazole ring, affected chemical yield, which then further improved when the solvent was changed to *t*-BuOH (entry 4, 5). The influence of the position of fluorous moiety on reactivity might be due to an electronic effect around the active site of the catalyst. Use of catalyst **7** demanded a higher reaction temperature because

of its low solubility in DMF. Unfortunately, the attempted construction of a quaternary carbon with catalyst **6** and substrate **2b** under the same conditions resulted in no product (entry 8).[8]

Table 1. Intramolecular Setter Reaction with Fluorous Thiazolium Salts



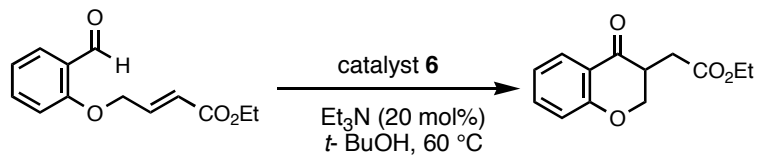
2a : R = H
2b : R = Me

3a : R = H
3b : R = Me

Entry	Substrate	Catalyst	Conditions	Yield (%)
1	2a	**1**	25 °C, 1.5 h, DMF	96
2	2a	**4**	80 °C, 2 d, DMF	23
3	2a	**5**	80 °C, 23 h, DMF	43
4	2a	**6**	40 °C, 24 h, DMF	66
5	2a	**6**	60 °C, 24 h, *t*-BuOH	82
6	2a	**7**	100 °C, 20 h, DMF	61
7	2a	**7**	80 °C, 24 h, *t*-BuOH	60
8	2b	**6**	70 °C, 23 h, *t*-BuOH	0*

* 2b was recovered in 63% yield.

Table 2. Reuse of Fluorous Catalyst



2a **3a**

Cycle	Catalyst **6** (mol%)	Yield (%)	Recovered catalyst (%)
1	20	82	69
2*	20	50 (58)**	74
3*	20	49 (71)**	96
4	19	50 (86)**	84
5	16	48 (64)**	70

* A small amount of catalyst **6** was added to maintain reaction ratio.
** The value in the parentheses is the recovery yield of the starting material.

Based on the above results, we investigated the potential for the use of the fluorous catalyst in multiple reaction cycles of the intramolecular Stetter reaction (Table 2). The recycling was examined as followed. The salicylaldehyde derivative **2a** (0.04 mmol) was treated with catalyst **6** (20 ~ 16 mol%) in the presence of Et_3N (20 mol%) at 60 °C in *t*-BuOH. After stirring for 24h, the reaction mixture was purified on a commercially available fluoro solid-phase to separate the desired product and catalyst **6**.[9] The recovered fluorous catalyst was used in the next reaction. As shown in

Table 2, this process was repeated 5 times and the catalyst still maintained the catalytic activity after the fifth cycle. Although a significant decrease of the catalytic activity was observed at the second and subsequent cycles, 70 % of the catalyst was recovered at the end of the last cycle.

In conclusion, we have demonstrated the preparation of fluorous catalysts and their application to the intramolecular Stetter reaction. The fluorous catalyst represents a good catalytic activity and retains catalytic activity on recovery.

ACKNOWLEDGEMENTS

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7. Spectral data of compound **6**: ^{1}H NMR (500 MHz, $CDCl_3$) δ11.37 (1H, s), 7.35-7.40 (6H, m), 7.21-7.26 (4H, m), 6.01 (2H, s), 4.53 (2H, s), 3.72 (2H, t, *J*=6.2), 3.08 (2H, t, *J*=6.2), 2.92-2.95 (2H, m), 2.40 (3H, s), 2.40 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ158.48, 141.65, 139.19, 135.34, 135.28, 131.86, 129.50, 129.38, 128.64, 128.47, 128.3373.31, 67.63, 57.01, 27.76, 12.51; ^{19}F NMR (470 MHz, $CDCl_3$) δ -80.61, -114.49, -121.58, -121.81, -122.60, -123.31, -126.00; IR(KBr) 2942, 1243, 1205, 1148, 750, 703, 657 cm^{-1}; Anal. Calcd for $C_{30}H_{25}BrF_{17}NOS$: C, 42.37; H, 2.96; N, 1. 65. Found: C, 42.20; H, 2.97; N, 1.64.

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9. The separation of catalyst was carried out with commercially available a fluorous SPE cartidge (Fluoro*Flash*®, 2 grams, 8 cc tube, Fluorous Technologies Incorporated). The reaction mixture was loaded onto the column and eluted with MeOH (10 mL) to give a desired compound. After treatment of 1N HCl (2 mL), the catalyst was eluted with MeOH (20 mL).