

FOUR-COMPONENT DOMINO REACTION FOR THE SYNTHESIS OF NOVEL 8-METHYL-9-SUBSTITUTED-2,10-DIARYL-2,3-DIHYDRO-10H-PYRANO[3,2-*e*][1,2,4,3]TRIAZAPHOSPHOLO[1,5-*c*]PYRIMIDINES

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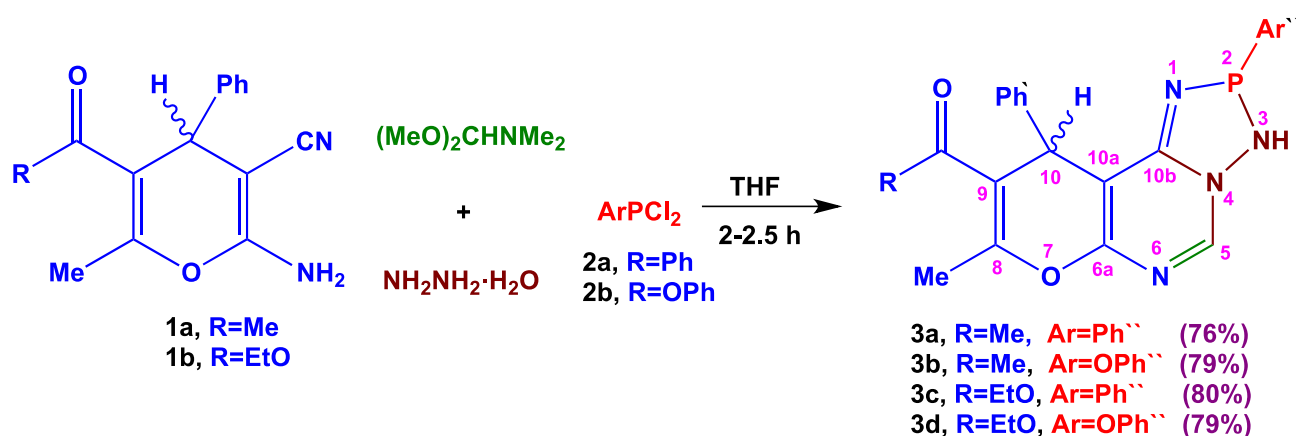
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Abstract – A novel four-component domino reaction for the synthesis of 8-methyl-9-substituted-2,10-diaryl-2,3-dihydro-10H-pyrano[3,2-*e*][1,2,4,3]triazaphospholo[1,5-*c*]pyrimidines has been established. The reaction was performed in THF using readily available 5-substituted-2-amino-6-methyl-4-phenyl-4H-pyran-3-carbonitrile, dimethylformamide dimethyl acetal, hydrazine hydrate and aryl dichlorophosphine. The simple and efficient one-pot four-component approach, catalyst free and mild reaction conditions made the present methodology a good synthetic procedure.

Nitrogen-containing heterocyclic compounds have always been a research hot topic because of their unique biochemical properties.^{1,2} In a valuable class of nitrogen containing molecular families, pyrimidine skeletons have attracted significant attention of chemists and biologists due to their prevalence in medicinal chemistry.^{3,4} Pyranopyrimidines, standing for a class of significant heterocycles, have a wide range of pharmacological activity and physiology activity, and are widely used in pharmaceutical, pesticide and other industries.⁵⁻⁷ Phosphorus-nitrogen compounds have gained considerable attention due to their biological and pharmacological effects such as antimicrobial,⁸ insecticidal,⁹ and herbicidal properties.¹⁰ Especially, different isomers of triazaphospholes possess multiple biological properties including antibacterial¹¹ and antineoplastic activities.¹² In recent years, we reported different strategies for the synthesis of P and N-heterocycles.¹³⁻¹⁸ In continuation of the project, we herein report an efficient approach for the synthesis of some novel functionalized pyrano[3,2-*e*][1,2,4,3]triazaphospholo[1,5-*c*]pyrimidines. The methodology depends on using readily available and inexpensive 5-substituted-2-amino-6-methyl-4-

phenyl-4*H*-pyran-3-carbonitrile, dimethylformamide dimethyl acetal, hydrazine hydrate and aryldichlorophosphine as substrates in one pot under mild reaction conditions.

5-Substituted-2-amino-6-methyl-4-phenyl-4*H*-pyran-3-carbonitrile (**1a,b**)¹⁹ was treated with dimethylformamide dimethyl acetal in dry THF at 55–60 °C for 30 min. After cooling, an equimolar amount of hydrazine hydrate was added and further stirred for another 30 min at room temperature. A solution of phenyldichlorophosphine (**2a**) or phenoxydichlorophosphine (**2b**) in THF was added to the mixture and heated at 55–60 °C for another 1–1.5 h. The progress of the reaction was monitored by thin layer chromatography. The reaction proceeded smoothly, and completed in total 2–2.5 h to afford the corresponding pyrano[3,2-*e*][1,2,4,3]triazaphospholo[1,5-*c*]pyrimidines **3a-d** in high yield (76-80%) (Scheme 1).

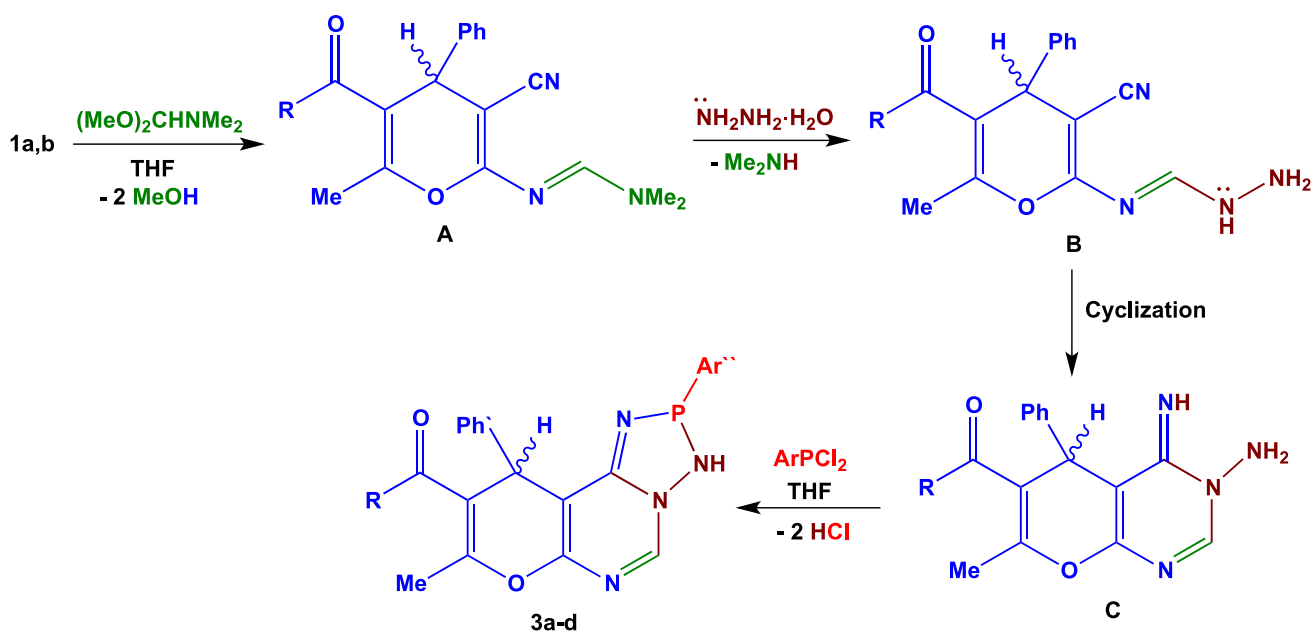


Scheme 1

All the novel products were determined from their IR, ¹H-NMR, ¹³C-NMR, and ³¹P-NMR spectra as well as mass spectrometry and elemental analysis. Compounds **3a-d** exhibited characteristic IR stretching frequencies in the regions 3120–3173 and 1663–1680 cm⁻¹ for NH and C=O, respectively. The aromatic protons of the phenyl rings of the products **3a-d** showed a complex multiplet at δ 6.77–8.19 ppm. The C₁₀-H proton signals appeared as singlets at δ 5.01–5.15 ppm. The C₅-H proton signals appeared at δ 8.37–8.54 ppm as singlets. The triazaphosphole NH protons resonated at δ 9.03–9.77 ppm as broad singlets. The methyl protons at position 8 were displayed as singlets at region δ 2.17–2.65 ppm. The carbon chemical shifts for C=O, C-5 and C-10 in the title compounds were observed at regions δ 160.5–182.5, 143.3–146.3 and 42.9–46.6 ppm, respectively. The ³¹P-NMR signals of the four products appeared in the region δ 24.3–28.9 ppm.

On the basis of our observation and information found in related literatures,^{20,21} we proposed a probable reaction mechanism for the formation of pyrano[3,2-*e*][1,2,4,3]triazaphospholo[1,5-*c*]pyrimidines that

occurred in one-pot and through three steps (Scheme 2). In the first step, the diethylenamine intermediate **A** was given after the attraction of substrate **1a,b** to dimethylformamide dimethyl acetal with the leaving of two MeOH molecules. Subsequently, the intermediate **A** underwent heterocyclization with hydrazine hydrate to afford the intermediates **B** followed by **C**. Then, the cyclization of the latter intermediate with aryldichlorophosphine through the attacking of nitrogen of amino and imino atom at the phosphorus atom gave the target products (Scheme 2).



Scheme 2

EXPERIMENTAL

The melting points were measured on a digital Stuart SMP-3 apparatus in an open capillary tube. Infrared spectra were measured on FT-IR spectrophotometer (Nicolet iS10) using KBr disks. ^1H - and ^{13}C -NMR spectra were determined on Gemini-300BB (400 and 100 MHz) spectrometer, using $\text{DMSO}-d_6$ as a solvent and TMS (δ) as an internal standard. ^{31}P -NMR spectra were measured on a Bruker (162 MHz) spectrophotometer using $\text{DMSO}-d_6$ as a solvent, TMS as an internal standard and 85% H_3PO_4 as an external reference. Mass spectra were recorded on direct probe controller inlet part to single quadrupole mass analyzer in (Thermo Scientific GCMS). Elemental microanalysis was performed on Perkin-Elmer 2400II at the Chemical War department, Ministry of Defense. The purity of the synthesized compounds was checked by thin layer chromatography (TLC) and elemental microanalysis.

General procedure for the synthesis of the target products **3a-d**.

A mixture of 5-substituted-2-amino-6-methyl-4-phenyl-4*H*-pyran-3-carbonitrile (**1a,b**) (2.5 mmol) and

dimethylformamide dimethyl acetal (0.30 mL, 2.5 mmol) in dry THF (25 mL) was heated at 55–60 °C for 30 min. The mixture was cooled into room temperature, then, hydrazine hydrate (0.13 mL, 2.5 mmol) was added in succession, and the mixture maintained at room temperature for 30 min. Finally, a solution of aryldichlorophosphine (2.5 mmol) in THF (3 mL) was added and the mixture was further heated at 55–60 °C for 1–1.5 h. After completion of the reaction, ice-cold water (75 mL) was added to the reaction mixture. The separated solid was filtered, washed with water, and dried. The product was recrystallized from suitable solvent to obtain final compounds.

9-Acetyl-8-methyl-2,10-diphenyl-2,3-dihydro-10H-pyrano[3,2-*e*][1,2,4,3]triazaphospholo[1,5-*c*]-pyrimidine (3a): Beige solid from EtOH in 76% yield; mp 258–260 °C. IR (KBr), (ν max, cm^{-1}): 3122 (NH), 1663 (C=O), 1610 (C=N), 1554 (C=C). $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): 2.05 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 5.01 (s, 1H, H-10), 6.94 (d, 1H, $J=8.0$ Hz, Ph-H), 7.32–7.38 (m, 3H, Ph-H), 7.40–7.44 (m, 2H, Ph-H), 7.49–7.55 (m, 2H, Ph-H), 7.79 (t, 1H, $J=7.6$ Hz, Ph-H), 7.98 (d, 1H, $J=7.2$ Hz, Ph-H), 8.39 (s, 1H, H-5), 9.77 (s, 1H, NH). $^{13}\text{C-NMR}$ (100 MHz, $\text{DMSO-}d_6$): 22.7 (CH_3), 25.7 (CH_3), 46.6 (C-10), 89.6 (C-10a), 110.2 (C-9), 123.8 (C-4''_{phenyl}), 125.2 (C-4'_{phenyl}), 126.7 (C-2',6'_{phenyl}), 127.9 (C-3',5'_{phenyl}), 128.5 (C-3'',5''_{phenyl}), 129.2 (C-2'',6''_{phenyl}), 130.5 (d, $J_{\text{PC}}=173$ Hz, C-1''_{phenyl}), 139.9 (C-1'_{phenyl}), 143.3 (C-5), 147.2 (C-10b), 154.4 (C-8), 156.7 (C-6a), 182.5 (C=O). $^{31}\text{P-NMR}$ (162 MHz, $\text{DMSO-}d_6$): 24.3 ppm. MS (m/z , I%): 402 (M^+ , 20%). Anal. Calcd for $\text{C}_{22}\text{H}_{19}\text{N}_4\text{O}_2\text{P}$ (402.39): C, 65.67%; H, 4.76%; N, 13.92%. Found: C, 65.49%; H, 4.71%; N, 13.79%.

9-Acetyl-8-methyl-2-phenoxy-10-phenyl-2,3-dihydro-10H-pyrano[3,2-*e*][1,2,4,3]triazaphospholo[1,5-*c*]pyrimidine (3b): Pale yellow solid from MeOH in 79% yield; mp 243–245 °C. IR (KBr), (ν max, cm^{-1}): 3173 (NH), 1680 (C=O), 1612 (C=N), 1554 (C=C). $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): 2.03 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 5.15 (s, 1H, H-10), 7.28–7.41 (m, 3H, Ph-H), 7.49–7.55 (m, 2H, Ph-H), 7.61–7.68 (m, 2H, Ph-H), 7.82 (t, 1H, $J=8.0$ Hz, Ph-H), 7.96 (d, 1H, $J=8.0$ Hz, Ph-H), 8.19 (d, 1H, $J=8.0$ Hz, Ph-H), 8.37 (s, 1H, H-5), 9.03 (s, 1H, NH). $^{13}\text{C-NMR}$ (100 MHz, $\text{DMSO-}d_6$): 22.1 (CH_3), 25.8 (CH_3), 45.5 (C-10), 91.4 (C-10a), 110.1 (C-9), 121.2 (C-4''_{phenyl}), 122.4 (C-2'',6''_{phenyl}), 124.8 (C-3'',5''_{phenyl}), 125.4 (C-4'_{phenyl}), 126.9 (C-2',6'_{phenyl}), 128.3 (C-3',5'_{phenyl}), 139.2 (C-1'_{phenyl}), 146.3 (C-5), 148.8 (C-10b), 151.3 (C-1''_{phenyl}), 153.9 (C-8), 155.4 (C-6a), 180.1 (C=O). $^{31}\text{P-NMR}$ (162 MHz, $\text{DMSO-}d_6$): 28.8 ppm. MS (m/z , I%): 418 (M^+ , 15%). Anal. Calcd for $\text{C}_{22}\text{H}_{19}\text{N}_4\text{O}_3\text{P}$ (418.12): C, 63.16%; H, 4.58%; N, 13.39%. Found: C, 62.95%; H, 4.49%; N, 13.22%.

Ethyl 8-methyl-2,10-diphenyl-2,3-dihydro-10H-pyrano[3,2-*e*][1,2,4,3]triazaphospholo[1,5-*c*]pyrimidine-9-carboxylate (3c): Pale yellow solid from MeOH in 80% yield; mp 222–223 °C. IR (KBr), (ν max, cm^{-1}): 3123 (NH), 1678 (C=O), 1596 (C=N), 1534 (C=C). $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): 0.77 (t, 3H, $J=6.8$ Hz, CH_3), 2.65 (s, 3H, CH_3), 3.91–3.98 (m, 2H, OCH_2), 5.04 (s, 1H, H-10), 6.77 (t, 1H, $J=7.2$ Hz, Ph-H), 6.86–6.89 (m, 3H, Ph-H), 7.04 (d, 1H, $J=8.0$ Hz, Ph-H), 7.17 (d, 1H, $J=7.6$ Hz, Ph-H),

7.23–7.25 (m, 3H, Ph–H), 7.28–7.31 (m, 1H, Ph–H), 8.50 (s, 1H, H–5), 9.03 (s, 1H, NH). ¹³C-NMR (100 MHz, DMSO-*d*₆): 15.1 (CH₃), 20.9 (CH₃), 44.2 (C–10), 60.1 (OCH₂), 93.1 (C–10a), 108.2 (C–9), 124.7 (C–4''_{phenyl}), 125.3 (C–4'_{phenyl}), 127.5 (C–2',6'_{phenyl}), 128.1 (C–3'',5''_{phenyl}), 128.7 (C–3',5'_{phenyl}), 129.9 (C–2'',6''_{phenyl}), 132.4 (d, *J*_{PC}=173 Hz, C–1''_{phenyl}), 139.9 (C–1'_{phenyl}), 147.2 (C–5), 148.7 (C–10b), 151.4 (C–8), 152.9 (C–6a), 160.5 (C=O). ³¹P-NMR (162 MHz, DMSO-*d*₆): 27.8 ppm. MS (*m/z*, I%): 432 (M⁺, 17%). Anal. Calcd for C₂₃H₂₁N₄O₃P (432.14): C, 63.89%; H, 4.90%; N, 12.96%. Found: C, 63.71%; H, 4.82%; N, 12.79%.

Ethyl 8-methyl-2-phenoxy-10-phenyl-2,3-dihydro-10H-pyrano[3,2-*e*][1,2,4,3]triazaphospholo[1,5-*c*]-pyrimidine-9-carboxylate (3d): Pale yellow solid from MeOH in 79% yield; mp 206–208 °C. IR (KBr), (*v* max, cm⁻¹): 3120 (NH), 1677 (C=O), 1595 (C=N), 1532 (C=C). ¹H-NMR (400 MHz, DMSO-*d*₆): 1.03 (t, 3H, *J*=8.0 Hz, CH₃), 2.17 (s, 3H, CH₃), 4.18 (q, 2H, *J*=8.0 Hz, CH₂), 5.09 (s, 1H, H–10), 7.00 (d, 1H, *J*=7.6 Hz, Ph–H), 7.09–7.15 (m, 4H, Ph–H), 7.22 (d, 1H, *J*=7.2 Hz, Ph–H), 7.51–7.58 (m, 2H, Ph–H), 7.82 (t, 1H, *J*=7.6 Hz, Ph–H), 8.00 (d, 1H, *J*=7.2 Hz, Ph–H), 8.54 (s, 1H, H–5), 9.46 (s, 1H, NH). ¹³C-NMR (100 MHz, DMSO-*d*₆): 13.6 (CH₃), 21.9 (CH₃), 42.9 (C–10), 59.7 (OCH₂), 90.7 (C–10a), 109.2 (C–9), 121.2 (C–4''_{phenyl}), 123.5 (C–2'',6''_{phenyl}), 124.8 (C–3'',5''_{phenyl}), 126.5 (C–4'_{phenyl}), 127.7 (C–2',6'_{phenyl}), 129.6 (C–3',5'_{phenyl}), 140.9 (C–1'_{phenyl}), 145.4 (C–5), 147.3 (C–10b), 152.1 (C–1''_{phenyl}), 156.1 (C–8), 157.4 (C–6a), 167.4 (C=O). ³¹P-NMR (162 MHz, DMSO-*d*₆): 28.9 ppm. MS (*m/z*, I%): 448 (M⁺, 10%). Anal. Calcd for C₂₃H₂₁N₄O₄P (448.13): C, 61.61%; H, 4.72%; N, 12.49%. Found: C, 61.49%; H, 4.63%; N, 12.31%.

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