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Synthetic studies on KF-alumina-catalysed reaction of substituted and unsubstituted aryl-oxoketene dithioacetals and 1*H*-pyrazone-5(4*H*)-one: a convenient synthesis of pyrazolo[3,4-*b*]pyridine and pyrazolo[1,5-*a*]pyrimidine

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ABSTRACT

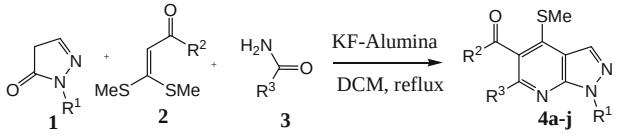
The procedures described herein provide a facile method for the synthesis of pyrazolo[3,4-*b*]pyridine and pyrazolo[1,5-*a*]pyrimidine by reacting N-substituted or unsubstituted-pyrazol-5(4*H*)-one, aryl-oxoketene dithioacetals and alkyl amide. The products were obtained in moderate to good yield. The effects of the solvents and substitution have also been described.

1. Introduction

The functionalized pyrazolo[3,4-*b*]pyridine and pyrazolo[1,5-*a*]pyrimidine are attractive compounds for drug discovery since many of these scaffolds exhibit excellent biological activities. For example, pyrazolo[3,4-*b*]pyridine derivatives have been evaluated for various biological applications ranging from being good vasodilators to hypotensive, anti-inflammatory, analgesics and antipyretic agents.[1] The pyrazolo[1,5-*a*] pyrimidines structural motif is found in a large number of pharmaceutical agents which exhibit diverse range of physiological activities such as antiepileptic agents,[2] anxiolytics[3] anti depressants[4] and as agents for treatment of sleep disorders[5] and oncolytics.[6] Therefore the development of simple methodologies for the synthesis of these highly functionalized derivatives is highly challenging in organic synthesis.

To address this challenge, the development of multi-component reaction method for the synthesis of these derivatives is of great interest owing to its high efficiency and selectivity. Although there are a wide range of methods available for the synthesis of pyrazolo[1,5-*a*] pyrimidines[7] and pyrazolo [3,4-*b*] pyridines,[8] very few of these procedures provide a simple method that could yield compounds with more structural diversities. In this Letter, we report a successful multi-component procedure for the synthesis of 1,4,5,6 tetrasubstituted pyrazolo[3,4-*b*] pyridine and a semi-conventional method for the synthesis of 5,6,7 trisubstituted pyrazolo[1,5-*a*] pyrimidines. The principal advantages, scope and limitations of the method are discussed.

The general method to prepare (1,4,6 tri-substituted-1*H*-pyrazolo[3,4-*b*]pyridi-6-yl) (aryl) methanone **4a–j** involves a three-component reaction between 1-substituted-1*H*-pyrazone-5(4*H*)-one **1**, substituted aryl-oxoketene dithioacetals **2** and alkyl amides **3** in presence of KF-alumina.[9] The reaction presumably involves Michael addition and condensation to yield the desired products. These reactions were attempted in range of solvents such as DMA, acetonitrile, DMF, THF and 1,4 dioxane. However, the desired products were obtained in DCM under refluxing conditions. The reactions studied took between 8 and 16 h for completion (Scheme 1). The reaction time increases when the steric demand of the reactant **1** increases (Table 1).



Scheme 1. Synthesis of (1,4,6 tri-substituted-1*H*-pyrazolo[3,4-*b*]pyridi-6-yl) (aryl) methanone.

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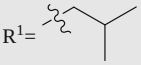
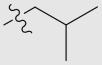
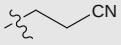
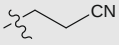
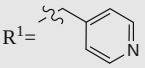
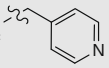
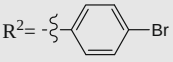
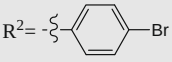
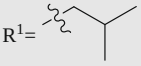
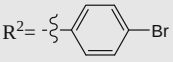
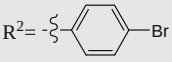
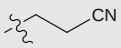
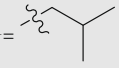
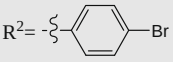
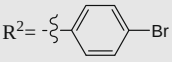
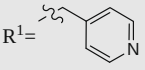
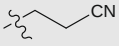
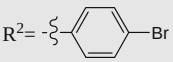
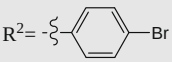
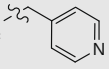
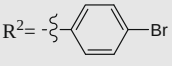
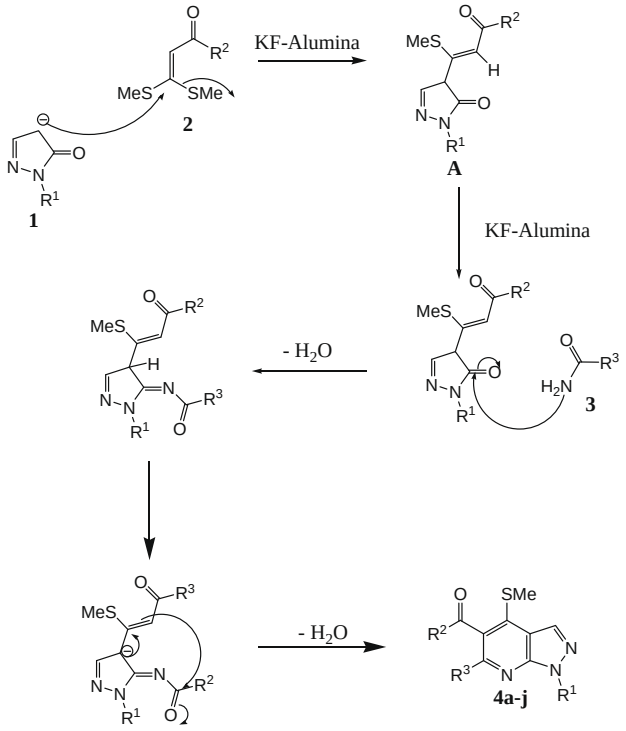
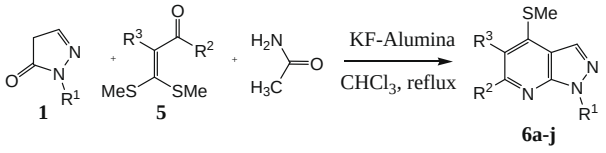
Table 1
Substituted fused pyridine and pyrimidines.

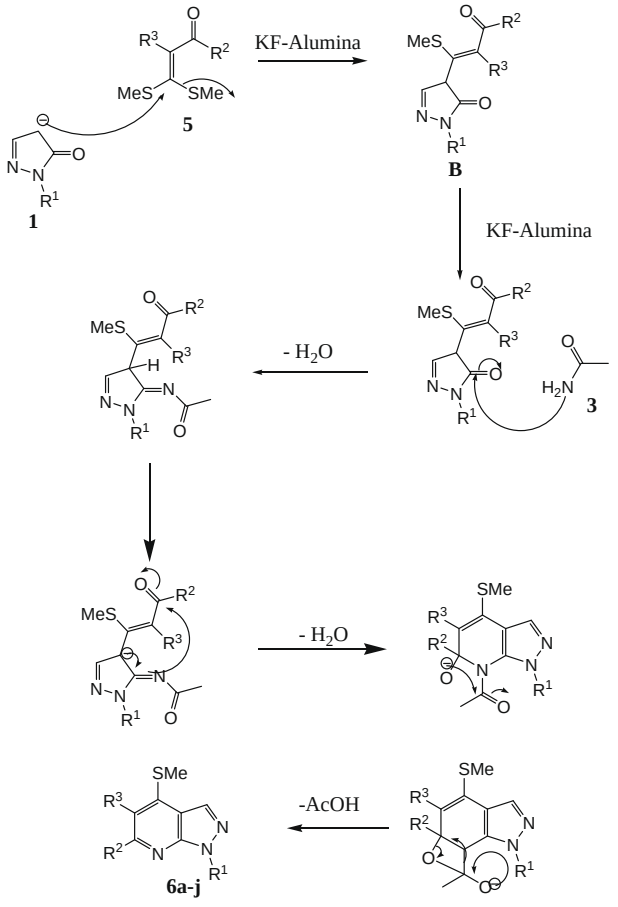
Entry	Product (**4a–j**)	Product (**6a–j**)	Product (**9a–j**)	Yields (%)
a	$R^1 = CH_3$ $R^2 = C_6H_5$ $R^3 = CH_3$	$R^1 = CH_3$ $R^2 = C_6H_5$ $R^3 = CH_3$	$R^1 = C_6H_5$ $R^2 = CH_3$	**4a** = 80 **6a** = 83 **9a** = 78
b	$R^1 = C_2H_5$ $R^2 = C_6H_5$ $R^3 = CH_3$	$R^1 = C_2H_5$ $R^2 = C_6H_5$ $R^3 = CH_3$	$R^1 = p$-Cl–C_6H_5 $R^2 = CH_3$	**4b** = 82 **6b** = 80 **9b** = 82
c	$R^1=$ 	$R^1=$ 	$R^1 = p$-NO_2–C_6H_5	**4c** = 81
	$R^2 = C_6H_5$ $R^3 = CH_3$	$R^2 = C_6H_5$ $R^3 = CH_3$	$R^2 = CH_3$	**6c** = 73 **9c** = 88
d	$R^1=$ 	$R^1=$ 	$R^1 = p$-Br–C_6H_5	**4d** = 83
	$R^2 = C_6H_5$ $R^3 = CH_3$	$R^2 = C_6H_5$ $R^3 = CH_3$	$R^2 = CH_3$	**6d** = 75 **9d** = 85
e	$R^1=$ 	$R^1=$ 	$R^1 = C_6H_5$	**4e** = 80
	$R^2 = C_6H_5$ $R^3 = CH_3$	$R^2 = C_6H_5$ $R^3 = CH_3$	$R^2 = C_2H_5$	**6e** = 77 **9e** = 79
f	$R^1 = CH_3$	$R^1 = CH_3$	$R^1 = p$-Cl–C_6H_5	**4f** = 81
	$R^2=$ 	$R^2=$ 	$R^2 = C_2H_5$	**6f** = 73
	$R^3 = C_2H_s$	$R^3 = C_2H_5$		**9f** = 81
g	$R^1=$ 	$R^1 = C_2H_5$	$R^1 = p$-NO_2–C_6H_5	**4g** = 79
	$R^2=$ 	$R^2=$ 	$R^2 = C_2H_5$	**6g** = 77
	$R^3 = CH_3$	$R^3 = C_2H_5$		**9g** = 81
h	$R^1=$ 	$R^1=$ 	$R^1 = p$-Br–C_6H_5	**4h** = 78
	$R^2=$ 	$R^2=$ 	$R^2 = C_2H_5$	**6h** = 67
	$R^3 = CH_3$	$R^3 = C_2H_5$		**9h** = 83
i	$R^1=$ 	$R^1=$ 		**4i** = 80
	$R^2=$ 	$R^2=$ 		**6i** = 79
	$R^3 = C_2H_5$	$R^3 = C_2H_5$		
j	$R^1 = CH_3$	$R^1=$ 		**4j** = 85
	$R^2 = C_6H_5$	$R^2=$ 		**6j** = 73
	$R^3 = C_2H_5$	$R^3 = C_2H_5$		



Scheme 2. Plausible mechanism for the synthesis (1,4,6 tri-substituted-1*H*-pyrazolo[3,4-*b*]pyridi-6-yl) (aryl) methanone.

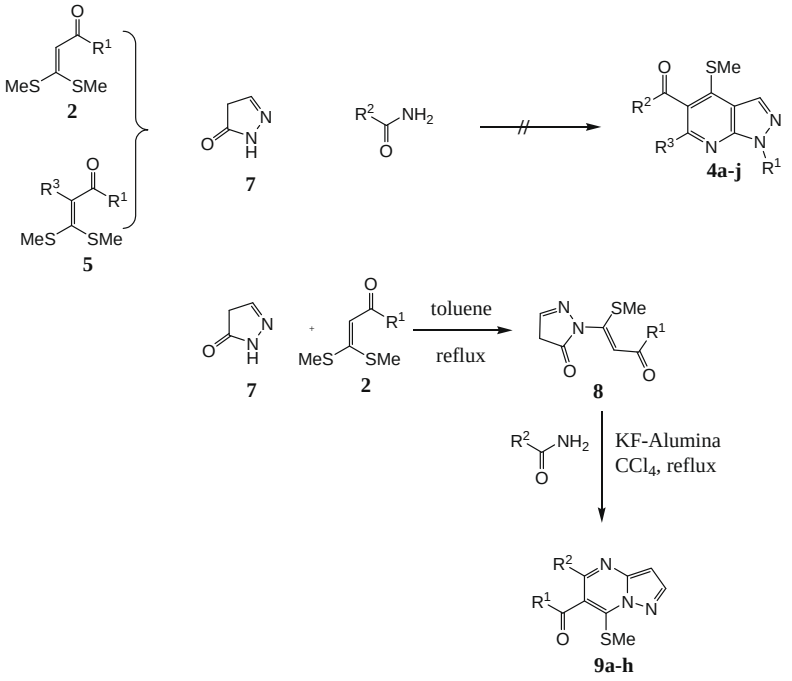


Scheme 3. Synthesis of 1,4,5,6 tetra-substituted pyrazolo[3,4-*b*]pyridine.



Scheme 4. Synthesis of 5,7,6 trisubstituted pyrazolo[1,5-*a*] pyrimidines.

A plausible mechanism for the formation of **4a–j** is outlined in Scheme 2. The reaction was initiated by Michael addition reaction between **1** and **2** to give the intermediate **A** which further condensed with **3** by abstraction of α-proton to give the



Scheme 5.

desired products. This may be concluded from the fact that when condensation of 1-methyl-pyrazol-5(4*H*)-one and 3,3-bis(methylthio)-1-phenylprop-2-en-1-one was carried out, 1-methyl-4-((*Z*)-1-(methylthio)-3-oxo-3-phenylprop-1-enyl)-pyrazol-5(4*H*)-one was isolated which on further treatment with acetamide afforded the desired product **4a**, thereby indicating that Michael addition is the first step in the three-component reaction.

In order to study whether a similar type of reaction occurred if the α-proton of the aryl oxoketene dithioacetals was unavailable, we carried out a three-component reaction of **1**, α-substituted aryl oxoketene dithioacetals **5** and acetamide in presence of KF-alumina.[10] Interestingly it was observed that the product obtained was 1,4,5,6 tetra-substituted pyrazolo[3,4-*b*]pyridine **6a–j** (Scheme 3). The plausible mechanism for the formation of **6a–j** is outlined in Scheme 4. The reaction was initiated by the Michael addition reaction between **1** and **5** to give 1,5 dicarbonyl **B** which further underwent condensation with acetamide to yield the desired products. The reaction presumably involves a Michael addition reaction to give 1,5 dicarbonyl which further underwent condensation with acetamide to yield **6a–j** (Table 1). The reactions were found to be solvent dependent and proceded only in $CHCl_3$ under refluxing condition. The reactions studied took between 12 and 24 h for completion.

It was further observed that the three-component reaction between 1*H*-pyrrol-2(3*H*)-one **7**, aryl oxoketene dithioacetal and acetamide yielded a complex mixture of products. However, when **7** was refluxed with **2** in toluene an addition product **8** was obtained, which when further refluxed with **3** in CCl_4 yielded 5,7,6 trisubstituted pyrazolo[1,5-*a*] pyrimidines **9a–h**[11] (Scheme 5).

In conclusion, we have developed efficient procedures for the synthesis of biologically active scaffolds by using a three-component KF-alumina-catalysed reaction.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.020.

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9. *Synthesis of* **4b**: A dry 100 mL flask was charged with 3,3-bis(methylthio)-1-phenylprop-2-en-1-one **2** (9.9 mmol), acetamides **3** (9 mmol), 1-ethyl-1*H*-pyrrol-2(3*H*)-one **1** (9 mmol), KF-alumina (1 g) and DCM (10 mL). The mixture was refluxed for 8–16 h. The reaction after completion (monitored by TLC), was cooled to room temperature, the solvent was evaporated in vacuum, and the crude product was purified by silica gel column chromatography using methanol–DCM (1:20) as eluent to obtain **4b**: mp 204–205 °C; IR (KBr) ν cm^{-1} 1685, 1630 and 1592; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 1.27 (t, 3H, J = 14.1 Hz), 2.32 (s, 3H), 2.58 (s, 3H), 3.47 (q, 2H, J = 8.5 Hz), 7.51–7.76 (m, 5H, aromatic), 8.05 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 13.2, 14.7, 18.5, 53.1, 107.6, 127.7, 128.1, 129.1, 132.1, 134.6, 135.7, 150.6, 153.5, 162.9, 195.1. MS (CI) m/z = 312.10 (M+1). Anal. Calcd for $C_{17}H_{17}N_3OS$: C, 65.57; H, 5.50; N, 13.49. Found: C, 65.55; H, 5.52; N, 13.51.
10. *Compound* **6c**: mp 174–175 °C; IR (KBr) ν cm^{-1} 1685, 1630 and 1592; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 0.99 (d, 6H, J = 6.5 Hz), 1.65–1.68 (m, 1H), 2.21 (s, 3H), 2.36 (s, 3H), 3.42 (d, 2H, J = 8.1 Hz), 7.41–7.85 (m, 5H, aromatic), 8.01 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 10.6, 13.7, 21.2, 25.9, 59.7, 103.7, 126.1, 126.7, 127.1, 128.7, 132.8, 134.9, 150.6, 153.9, 157.7.MS (CI) m/z = 312.16 (M+1). Anal. Calcd for $C_{18}H_{21}N_3S$: C, 69.43; H, 6.80; N, 13.49. Found: C, 69.39; H, 6.80; N, 13.47.
11. *Compound* **9a**: mp 245–246 °C; IR (KBr) ν cm^{-1} 1685, 1630 and 1592; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.24 (s, 3H), 2.41 (s, 3H), 6.74 (d, 1H, J = 9.1 Hz), 7.42–7.71 (m, 5H, aromatic), 8.12 (d, 1H, J = 9.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 13.1, 19.2, 98.3, 126.3, 127.3, 129.9, 130.9, 134.6, 135.9, 147.3, 159.8, 166.7, 195.9. MS (CI) m/z = 284.41 (M+1). Anal. Calcd for $C_{15}H_{13}N_3OS$: C, 63.58; H, 4.62; N, 14.83. Found: C, 63.56; H, 4.60; N, 14.80.