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Reactivity of the –C(Cl)=C–C=N– moiety towards $AlCl_3$-induced C–C bond forming reactions: a new synthesis of 7-(hetero)aryl-substituted pyrazolo[1,5-*a*]pyrimidines

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ABSTRACT

The reactivity of the –C(Cl)=C–C=N– moiety towards an $AlCl_3$-induced C–C bond forming reaction was investigated through the reaction of 7-chloro-5-phenyl-pyrazolo[1,5-*a*]pyrimidine with arenes and heteroarenes. This study furnished a novel and highly selective methodology for the preparation of 7-(hetero)aryl substituted-pyrazolopyrimidines in good to excellent yields under mild reaction conditions.

We first describe the $AlCl_3$-induced C–C bond forming reaction between 7-chloro-5-phenyl-pyrazolo[1,5-*a*]pyrimidine and (hetero)arenes, such reactions being only known for using transition-metal catalysts.

Over the last 20 years, the pyrazolo[1,5-*a*]pyrimidine framework, a member of [5,6]-fused bicyclic heterocycles, has been a versatile scaffold for various pharmacological studies.[1–8] Apart from their utility for several disease targets, pyrazolo[1,5-*a*]pyrimidines have shown enormous synthetic value in the preparation of various drugs and bio-active molecules. This is exemplified by the usage of 3-cyanomethyl and 3-cyano derivatives of 7-(hetero)aryl-pyrazolo[1,5-*a*]pyrimidines (**A** and **B**, Fig. 1) as key intermediates in the synthesis of a number of drugs.[9–12] Also, 3-bromo-7-(hetero)aryl-pyrazolo[1,5-*a*]pyrimidines (**C**, Fig. 1) have been a key synthetic precursor for ω-functionalized 3-alkynylpyrazolo[1,5-*a*]-pyrimidines.[13] Because of their wide pharmaceutical and synthetic importance, a number of methods have been developed for the synthesis of appropriately substituted pyrazolo[1,5-*a*]pyrimidines.[14–19] However, none of these methods were found to be convenient and general for the preparation of 7-(hetero)aryl pyrazolopyrimidines (**D**, Fig. 1). Recently, transition metal-mediated C–C bond forming reactions have become a powerful tool in organic synthesis. Accordingly, 7-chloro-5-phenyl-pyrazolo[1,5-*a*]-pyrimidine was coupled with (a) arylboronic acids under Suzuki conditions or (b) an organometallic reagent such as ArZnI in the presence of a Pd-catalyst to afford the compound **D**.[20] While these methodologies afforded **D** in good yields, they often required the use of expensive catalysts and reagents. Additionally, in many

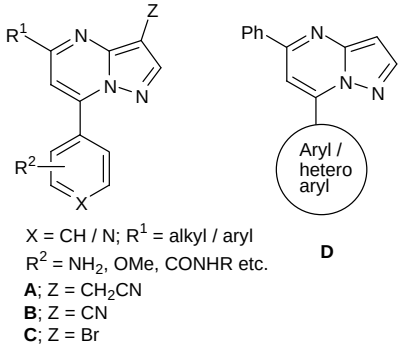

Figure 1. Examples of pyrazolopyrimidine precursors for the synthesis of various drugs.

cases the required boronic acids or organo-zinc reagents are either not available commercially or their preparations often require cumbersome procedures. More recently, $AlCl_3$-induced heteroarylation of arenes and heteroarenes has been reported as an alternative but less expensive strategy for the synthesis of various nitrogen containing heterocyclic compounds.[21–23] This strategy involved the construction of a C–C bond via exploiting the reactivity of a chloro group attached to the azomethine carbon [e.g., =C–C(Cl)=N–] in the presence of $AlCl_3$. While a variety of heteroaryl chlorides containing the =C–C(Cl)=N– moiety have been utilized successfully earlier,[24,25] to the best of our knowledge the reactivity of a chloride containing the –C(Cl)=C–C=N– moiety towards an $AlCl_3$-induced C–C bond forming reaction has not been examined. We anticipated that the complexation of $AlCl_3$ with the nitrogen of the –C(Cl)=C–C=N– moiety would activate the chloro group

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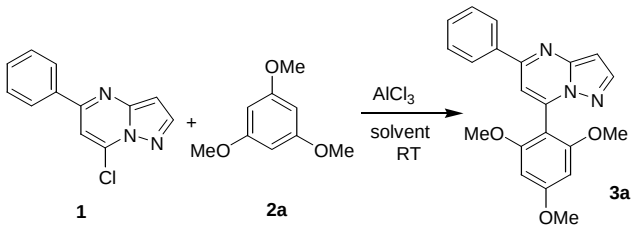


Scheme 1. $AlCl_3$-induced heteroarylation of 1,3,5-trimethoxybenzene (**2a**) with **1**.

Table 1
Heteroarylation of **2a** with **1** under various conditions

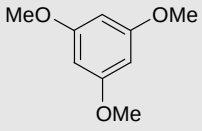
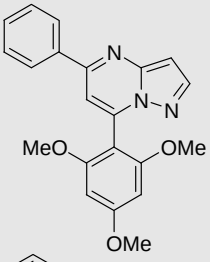
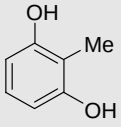
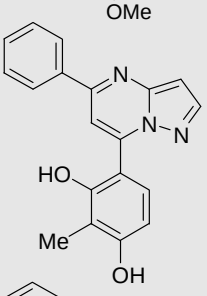
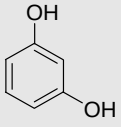
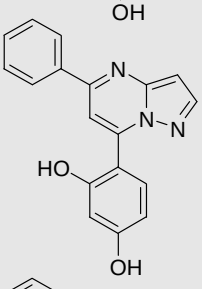
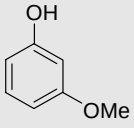
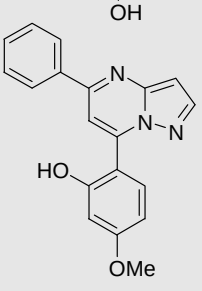
Entry	Solvent	Time (h)	Yield[a] (%)
1	$ClCH_2CH_2Cl$	15	89
2	CH_2Cl_2	48	74
3	$CHCl_3$	54	70
4	CH_3CN	24	74
5	EtOAc	32	77
6	THF[b]	12	62
7	Toluene	72	No reaction

[a] Yield of isolated products.
[b] The reaction was carried out at 60 °C.

to facilitate a nucleophilic attack by arenes or heteroarenes at the chlorine bearing carbon atom. Herein, we report the first (hetero)arylation of 7-chloro-5-phenyl-pyrazolo[1,5-*a*]pyrimidine in the presence of $AlCl_3$ amenable for the preparation of compounds of potential pharmacological interest.

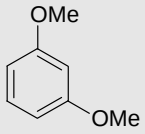
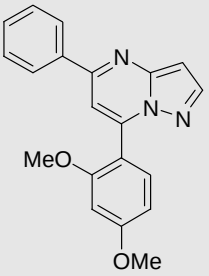
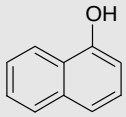
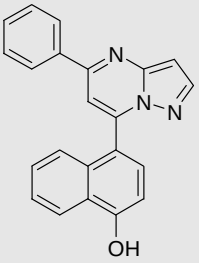
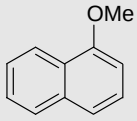
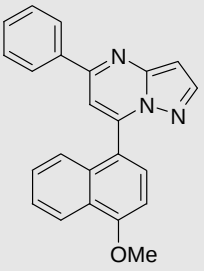
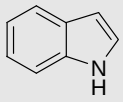
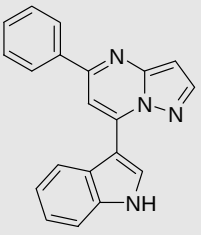
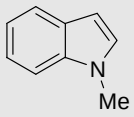
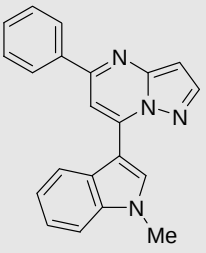
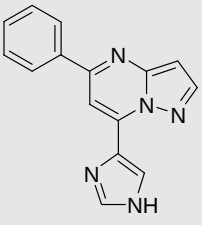
The key compound that is, 7-chloro-5-phenyl-pyrazolo[1,5-*a*]pyrimidine (**1**) required for our study was prepared via the reaction of 3-aminopyrazole with ethyl benzoylacetate in acetic acid under reflux for 3 h followed by chlorination of the resulting compound (i.e., 5-phenyl-4*H*-pyrazolo[1,5-*a*]pyrimidin-7-one) in $POCl_3$ in the presence of pyridine at room temperature for 3 days.[26] In our initial approach 1,3,5-trimethoxybenzene **2a**, chosen as an arene component was reacted with **1** (Scheme 1) and the results of our initial studies are summarized in Table 1. Thus a mixture of **1** (1.0 equiv), **2a** (1.0 equiv) and $AlCl_3$ (1.2 equiv) in dichloroethane (5 ml) was stirred at room temperature (25 °C). Both the reactants were consumed completely after 15 h and the desired 5-phenyl-7-(2,4,6-trimethoxy-phenyl)-pyrazolo[1,5-*a*]pyrimidine **3a** was isolated in 89% yield (Table 1, entry 1,). Encouraged by this result, we then decided to examine the effect of time, temperature and solvents on this heteroarylation process. It was observed that the longer reaction time (48 h) did not improve the product yield (data not shown) whereas the reaction was completed within 2 h when

Table 2
Synthesis of 7-(hetero)aryl-substituted pyrazolo[1,5-*a*]pyrimidines (**3**)

S. No	Reactant (2)	Product (**3**)	Conditions	Yield[a] (%)
1	 **2a**	 **3a**	rt 15 h 80 °C 2 h	89 87
2	 **2b**	 **3b**	rt 20 h 80 °C 7 h	86 83
3	 **2c**	 **3c**	rt 20 h 80 °C 13 h	84 82
4	 **2d**	 **3d**	rt 16 h 80 °C 10 h	84 82

(*continued on next page*)

Table 2 (*continued*)

S. No	Reactant (2)	Product (**3**)	Conditions	Yield[a] (%)
5	 **2e**	 **3e**	rt 13 h 80 °C 8 h	86 85
6	 **2f**	 **3f**	rt 36 h 80 °C 24 h	32 80
7	 **2g**	 **3g**	rt 24 h 80 °C 9 h	45 84
8	 **2h**	 **3h**	rt 21 h 80 °C 3 h	87 85
9	 **2i**	 **3i**	rt 16 h 80 °C 3 h	90 89
10	 **2j**	 **3j**	rt 33 h 80 °C 20 h	35 88

[a] Yield of isolated products.

carried out at 80 °C (see later, Table 2). Nevertheless, in order to maintain the milder nature of reaction conditions we decided to continue our studies at room temperature. To identify the best suitable solvent, the heteroarylation of **2a** was carried out in a variety of solvents without changing other factors and conditions as shown in Scheme 1. Reactions proceeded well in dicholorome-

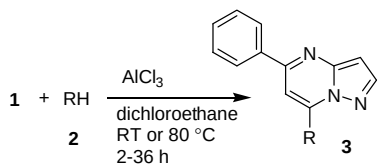
thane, chloroform, acetonitrile, ethylacetate and THF but required varied reaction times for completion (Table 1, entries 2–6). Yields of isolated products were found to be comparable in all these solvents except THF. Toluene was found to be ineffective for the reaction of **1** with **2a** (Table 1, entry 7). Thus, dichloroethane was found to be the best solvent for the heteroarylation of **2a** with **1**.

Having established the optimum condition, we then decided to examine the reactivity of heteroaryl chloride **1** with other arenes and heteroarenes. Accordingly, a number of arenes were reacted with **1** (Scheme 2) and the results are summarized in Table 2. Arenes such as 2-methyl-benzene-1,3-diol (**2b**), benzene-1,3-diol (**2c**), 3-methoxy-phenol (**2d**), 1,3-dimethoxybenzene (**2e**), 1-naphthol (**2f**) and 1-methoxynaphthalene (**2g**) were employed successfully to afford the desired products **3b**–**3g** (Table 2, entries 2–7) in good yields.[27,28] While the reactions were carried out at room temperature in most cases, the heteroarylation of naphthalene derivatives for example, **2f** and **2g** however required a higher temperature that is, 80 °C (Table 2, entry 6 and 7). The free phenolic hydroxyl group was well tolerated in the case of **2b**, **2c**, **2d** and **2f** (Table 2, entries 2–4 and 6) and heteroarylation occurred at the ring carbon rather than oxygen. The use of heteroarenes such as indole (**2h**), *N*-methylindole (**2i**) and imidazole (**2j**) afforded the corresponding products **3h**, **3i** and **3j** in good yields (Table 2, entries 8–10).

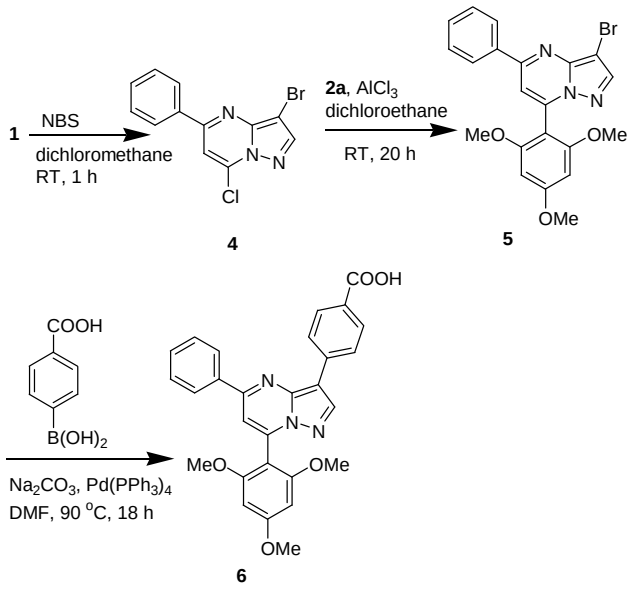
We have shown that 7-chloro pyrazolo[1,5-*a*]pyrimidine participated in $AlCl_3$-induced C–C bond forming reactions smoothly with a variety of commercially available arenes and heteroarenes. Besides the preparation of **3f**, **3g** and **3j**, which require elevated temperatures, the reaction proceeds equally well at room temperature or 80 °C. In order to extend the scope and application of this process, 3-bromo-7-chloro-5-phenyl pyrazolo[1,5-*a*]pyrimidine (**4**), prepared by treating compound **1** with NBS[26] in dichloromethane was reacted with trimethoxybenzene (**2a**) in the presence of $AlCl_3$ at rt (Scheme 3). The chloro group was replaced by the arene smoothly without affecting the bromo group affording the corresponding product **5** in good yield (79%). The observed selectivity of the $AlCl_3$-induced heteroarylation reaction towards chloro over bromo is remarkable and allows the preparation of appropriate bromo derivatives amenable for further functionalizations.[13] Thus, compound **5** was coupled with 4-carboxyphenylboronic acid under the Suzuki reaction condition to afford compound **6** in 67% yield (Scheme 3), demonstrating the potential of the present process for the preparation of diversity based pyrazolopyrimidine analogues of potential pharmacological interest.

Mechanistically, the present C–C bond forming reaction seems to proceed via complexation of the nitrogen of the six-membered ring with $AlCl_3$ to activate the chloro group. This facilitates a nucleophilic attack by arenes or heteroarenes at the chlorine bearing carbon atom (Fig. 2). However, the reactivity of the chloro group seemed to have been enhanced further by the adjacent nitrogen present at the junction of the 6- and 5-membered ring (Fig. 2). This perhaps explains the fact that unlike other heteroaryl halides[21–23] the reaction of **1** with **2** proceeds at room temperature.

In conclusion, the methodology described above illustrates the usefulness of 7-chloropyrazolo[1,5-*a*]pyrimidine as an efficient heteroarylating agent for arenes and heteroarenes in the presence of $AlCl_3$ in a one-pot reaction. The methodology is free from the formation of homocoupled products as byproducts, a common side



Scheme 2. $AlCl_3$-induced heteroarylation of **2** with **1**.



Scheme 3. Synthesis of compound **6**.

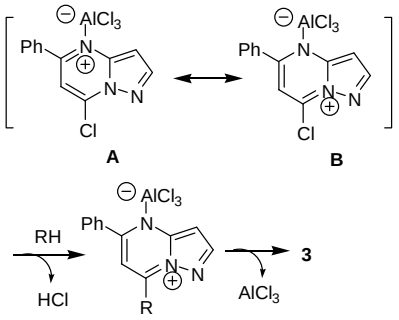


Figure 2. Proposed mechanism for $AlCl_3$-induced heteroarylation of **2** with **1**.

reaction often observed with transition-metal-catalyzed reactions and therefore may have advantages over the transition-metal-mediated process for the synthesis of 7-(hetero) aryl-pyrazolo-[1,5-*a*]pyrimidines especially on a large scale. We believe that the methodology would find wide applications in the synthesis of diversity-based pyrazolopyrimidines of potential medicinal value.

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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.2008.11.010.

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27. *Typical procedure for the synthesis of 7-(hetero)aryl-5-phenyl-pyrazolo[1,5-a]-pyrimidine* (**3a**–**j**): A mixture of 7-chloro-5-phenyl-pyrazolo[1,5-*a*]-pyrimidine (**1**, 1.0 equiv), arene (**2a**–**g**) or heteroarene (**2h**–**j**) (1.0 equiv) and anhydrous $AlCl_3$ (1.2 equiv) in dichloroethane (5 mL) was stirred according to the conditions mentioned in Table 2. After completion of the reaction, the mixture was poured into ice-cold water (15 mL), stirred for 10 min and then extracted with ethyl acetate (3 × 5 mL). The organic layers were collected, combined, washed with water (3 × 10 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography to afford the expected products.
28. *Spectral data for selected compounds*: compound **3a**: yellow solid; mp 182.6 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.24–8.21 (m, 2H), 8.06 (d, J = 2.2 Hz, 1H), 7.53–7.51 (m, 4H), 6.75 (d, J = 2.3 Hz, 1H), 6.42 (s, 2H), 3.89 (s, 3H, OCH_3), 3.66 (s, 6H, OCH_3); ν_{max} (KBr, cm^{-1}): 1621, 1587; Mass (ESI method, *i*-butane): 362 (M^++1, 100%); ^{13}C NMR (75 MHz, DMSO-d_6) 162.9, 158.8 (2C), 154.3, 148.4, 144.3, 142.3, 136.7, 130.3, 128.9 (2C), 127.1 (2C), 107.8, 101.9, 96.1, 91.0 (2C), 55.8 (2C, OCH_3), 55.5 (OCH_3); HPLC purity 98.90%; compound **3b**: yellow solid; mp 197.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.06 (s, 1H), 8.23 (d, J = 2.5 Hz, 1H), 8.14–8.11 (m, 2H), 7.57–7.51 (m, 3H), 7.43 (s, 1H), 7.36 (d, J = 8.6 Hz, 1H), 6.83 (d, J = 2.5 Hz, 1H), 6.62 (d, J = 8.6 Hz, 1H), 5.22 (s, 1H), 2.29 (s, 3H, CH_3); ν_{max} (KBr, cm^{-1}): 1604, 1549; Mass (ESI method, *i*-butane):318.1 (M^++1, 100%); ^{13}C NMR (75 MHz, $CDCl_3$) 158.4, 157.2, 156.6, 150.0, 147.9, 144.7, 137.3, 130.5, 129.3, 129.0 (2C), 127.5 (2C), 115.1, 113.0, 109.0, 106.9, 97.8, 8.7; HPLC purity 99.16%; compound **3g**: light brown solid; mp 153.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (d, J = 8.3 Hz, 1H), 8.16–8.08 (m, 3H), 7.73 (d, J = 7.8 Hz, 1H), 7.52–7.39 (m, 7H), 6.98 (d, J = 8.0 Hz, 1H), 6.85 (d, J = 2.2 Hz, 1H), 4.09 (s, 3H, OCH_3); ν_{max} (KBr, cm^{-1}): 1606, 1584, 1545; Mass (ESI method, *i*-butane):352.3 (M^++1, 100%); ^{13}C NMR (75 MHz, DMSO-d_6) 156.7, 154.9, 148.7, 146.4, 144.9, 136.7, 131.2, 130.4, 129.2 (2C), 128.9 (2C), 127.3 (2C), 125.7, 125.2, 124.6, 121.9, 121.6, 107.0, 103.9, 96.7, 55.9; HPLC purity 99.91%.