Novel One-Pot Three Component Reaction for the Synthesis of [2-(Alkylsulfanyl)imidazo[1,2-*a*]pyridin-3-yl](aryl)methanone

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A one-pot, three-component reaction between pyridine, phenacyl bromide, and thiocyanate is described. The reaction afforded the corresponding special type of fully substituted imidazo[1,2-*a*]pyridine derivatives in good yields without using any catalyst or activation.

1. Introduction

A major challenge of modern drug discovery is the design of highly efficient chemical reaction sequences that provide maximum structural complexity and diversity with a minimum number of synthetic steps to assemble compounds with interesting properties.[1] Great efforts have been focused on synthesizing libraries of small heterocyclic molecules because of their high degree of structural diversity and extensive utility as therapeutic agents.[2] The development of new, rapid, and clean synthetic routes toward focused libraries of such compounds is therefore of great importance to both medicinal and synthetic chemists.[3] Undoubtedly, synthetic strategies involving multicomponent reactions (MCRs) have manifested themselves as a powerful tool for the rapid introduction and expansion of molecular diversity.[4] Consequently, the design and development of new MCR routes for the generation of heterocycles receives growing interest.[5]

Synthesis of imidazo[1,2-*a*]pyridines and their analogues has attracted significant attention in recent years as this class of compounds exhibits a broad range of useful pharmacological activity, including antibacterial,[6] antifungal,[7] antiviral,[8] antiulcer,[9] and anti-inflammatory behaviors.[10] They have also been characterized as selective cyclin-dependent kinase inhibitors,[11] calcium channel blockers,[12] b-amyloid formation inhibitors,[13] and benzodiazepine receptor agonists,[14] and they constitute a novel class of orally active nonpeptide bradykinin B_2 receptor antagonists.[15] Drug formulations containing imidazo[1,2-*a*]pyridines such as alpidem (anxiolytic), zolpidem (hypnotic), and zolimidine (anti-ulcer) are currently available (Figure 1).

The pharmacological profile of imidazo[1,2-*a*]pyridines is shown to be critically dependent on the nature of the substituents at the 2 and 3 positions.[16] Thus, there is a definite need to develop a more structurally flexible method for the synthesis of this class of compounds.

So far, several synthetic methods have been reported for the preparation of imidazo[1,2-a]pyridine ring systems. The most common approach for the synthesis of imidazo[1,2-a]pyridines involves construction of the imidazole ring by reactions of 2-aminopyridines with glyoxal trimer dehydrate,[17] α-halocarbonyl compounds,[18] and other 1,2-dielectrophilic compounds.[19] 2-Aminopyridines have also been used in a one-pot condensation reaction with aldehydes and isonitriles to construct this class of compounds.[20] In another method they have been prepared by reactions of 2-chloropyridines with 1,2,3-triazoles and subsequent elimination of nitrogens.[21] This class of compounds has also been prepared via pyridinium salts such as 1-[1-substituted 2,2-bis(methylthio)ethenyl]pyridinum,[22] 2-halo-1-alkylpyridinium,[23] and 2-halo-1-phenacyl pyridinum[24] salts. Approaches based on the use of substituted imidazoles as starting materials to construct the imidazopyridine nucleus, via cyclization of 1-(2-alkynyl)-2-aminomethylimidazoles and reactions of (arylacetyl)imidazoles with acetylenedicarboxylic esters, have also been described.[25] However, most of these methods suffer from lengthy sequences, low overall yields, and limited ability to vary substituents or use relatively inaccessible starting materials.

Considering the above reports, the development of new and simple synthetic methods for the efficient preparation of the heterocycles containing imidazo[1,2-*a*]pyridine ring fragments will be a beneficial and interesting challenge. As part of our current studies on the development of efficient methods for the preparation of heterocyclic compounds,[26] herein, we report a novel one-pot and three-component synthesis of imidazo[1,2-*a*]pyridines with 2-alkylsulfanyl and aroyl substituents at 2 and 3 positions. The notable advantages offered by this method are readily available starting materials, simple operation, and good yields of the products.

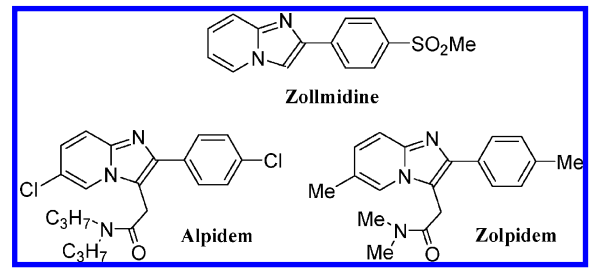

Figure 1

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Scheme 1. Model Reaction

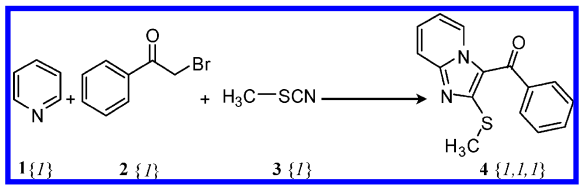


Table 1. Model Reaction, Conditions, and Yield[a]

entry	conditions	time (h)	yield (%)
1	solvent-free (100 °C)	12	42
2	CH_3CN (reflux)	12	21
3	water (reflux)	12	0
4	Toluene (reflux)	12	78
5	EtOH (reflux)	12	0
7	THF (reflux)	12	14

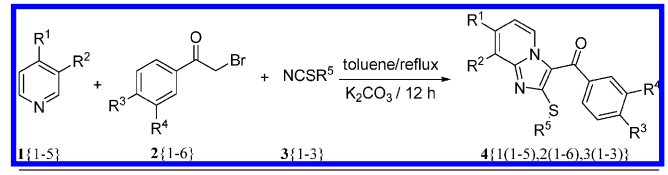
[a] Pyridine (1.2 mmol), phenacyl bromide (1.2 mmol), methyl thiocyanate (1 mmol), and K_2CO_3 (2 mmol).

2. Results and Discussion

First, to achieve suitable conditions for the synthesis of imidazo[1,2-*a*]pyridines **4**, we tested the reaction of pyridine **1**{*1*}, phenacyl bromide **2**{*1*}, and methyl thiocyanate **3**{*1*} as a simple model substrate in various solvents and under solvent-free classical heating conditions in the presence of potassium carbonate (Scheme 1). The results are shown in Table 1. It was found that toluene is a solvent of choice for the reaction, and the desired product was obtained in good yield and high purity (entry 4).

After optimization of the reaction conditions, to delineate this approach, particularly in regard to library construction, this methodology was evaluated by using different pyridines, phenacyl bromides, and thiocyanates. Five commercially available pyridines **1**{*1*−*5*}, six substituted phenacyl bromides **2**{*1*−*6*}, and three commercially available thiocyanates **3**{*1*−*3*} were chosen for the library validation, and 20 examples were selected as synthetic targets from 90 (theoretical library size) (Figure 2). Corresponding imidazo[1,2-*a*]pyridine derivatives **4** were synthesized by the one pot, three-component condensation of pyridines **1**, phenacyl bromides **2**, and thiocyanates **3** in good yields in refluxing toluene in the presence of potassium carbonate for 12 h. The reaction can be represented as in Table 2. To the best of our knowledge, this new procedure provides the first example of an efficient and three-component method for the synthesis of this class of imidazo[1,2-*a*]pyridine derivatives.

Table 2. Synthesis of Imidazo[1,2-*a*]pyridine Derivatives **4**



entry	yield (%)[a]	R^1	R^2	R^3	R^4	R^5
4{*1,1,1*}	78	H	H	H	H	Me
4{*1,1,2*}	76	H	H	H	H	Et
4{*1,2,1*}	81	H	H	Cl	H	Me
4{*1,2,2*}	74	H	H	Cl	H	Et
4{*2,1,1*}	82	Et	H	H	H	Me
4{*2,1,2*}	79	Et	H	H	H	Et
4{*2,2,1*}	77	Et	H	Cl	H	Me
4{*2,3,1*}	83	Et	H	Br	H	Me
4{*2,3,3*}	79	Et	H	Br	H	Bn
4{*2,4,1*}	86	Et	H	MeO	H	Me
4{*2,6,1*}	90	Et	H	H	MeO	Me
4{*3,2,1*}	78	Bn	H	Cl	H	Me
4{*3,4,1*}	84	Bn	H	MeO	H	Me
4{*3,4,2*}	81	Bn	H	MeO	H	Et
4{*4,1,1*}	75	H	Me	H	H	Me
4{*4,1,2*}	74	H	Me	H	H	Et
4{*4,3,1*}	77	H	Me	Br	H	Me
4{*4,3,3*}	72	H	Me	Br	H	Bn
4{*5,5,1*}	78	H	Cl	H	Br	Me
4{*5,5,2*}	81	H	Cl	H	Br	Et

[a] Isolated yields.

Given the large number of commercially available pyridines and the easy access to phenacyl bromides and thiocyanates, the present method should be applicable to synthesis of libraries with high diversity. We expect this method to find extensive application in the field of combinatorial chemistry, diversity-oriented synthesis, and drug discovery.

Finally, to further explore the potential of this protocol for heterocyclic synthesis, we investigated a reaction involving chloroacetonitrile **5** and obtained 2-(methylsulfanyl)imidazo[1,2-*a*]pyridine-3-yl cyanide derivative **6** in good yield (Scheme 2). Furthermore, the 2-sulfur atom of **4**{*2,3,1*} can be oxidized to yield compound **7** and shows the possibility

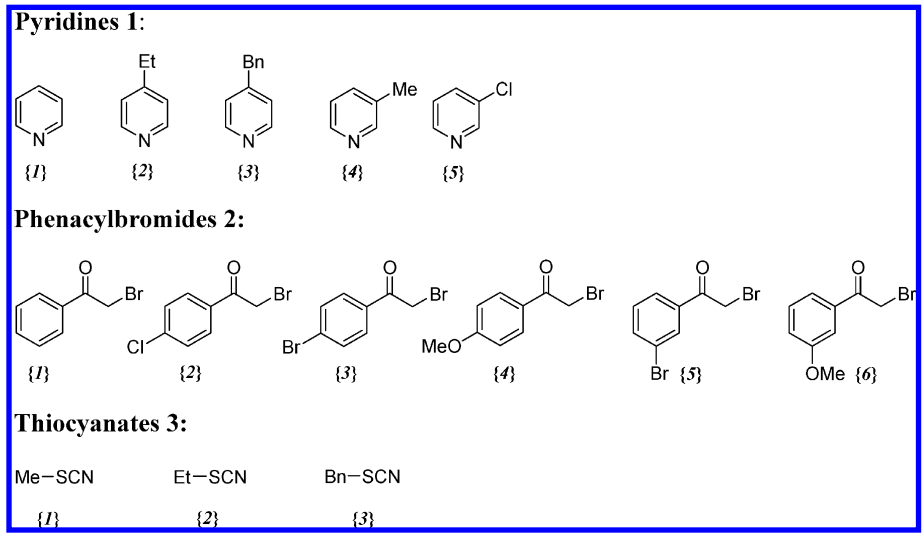
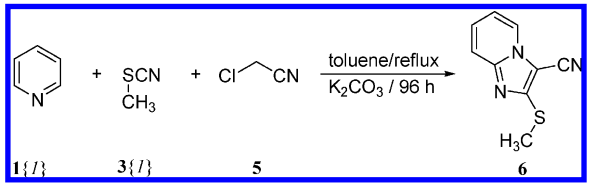
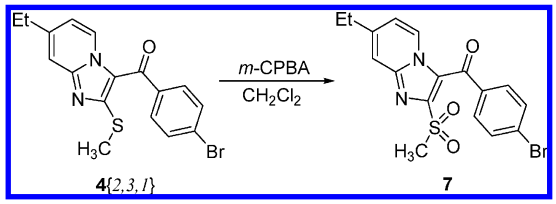


Figure 2. Diversity of reagents.

Scheme 2. Synthesis of 2-(Methylsulfanyl)imidazo[1,2-*a*]-pyridine-3-yl Cyanide **6**



Scheme 3. Possible Derivatizations of Imidazo[1,2-*a*]-pyridine **4**



of a subsequent functionalization of the imidazo[1,2-*a*]pyridine ring system (Scheme 3).

Although the mechanism of this reaction has not been established experimentally, a reasonable mechanism is shown in the Supporting Information. It is worthy of mention that in the 3-substitued pyridines only the *ortho*-position of the substituents was attacked by the imine anion to form an imidazole ring.[27]

Compounds **4**, **6**, and **7** are stable solids whose structures were established by IR, ^{1}H NMR, ^{13}C NMR, and EI-MS spectroscopy.

In conclusion, we have demonstrated an efficient and simple method for the preparation of imidazo[1,2-*a*]pyridine derivatives using readily available starting materials. Prominent among the advantages of this new method are novelty, operational simplicity, and good yields. Further reactivity studies and synthetic applications of this methodology are in progress in our laboratory.

Synthesis of 4{1,1,1}. ***Caution!*** *Severe toxicity will occur with doses of less than 1 g of thiocyanates. When strongly heated or on contact with acids or acid fumes, they emit highly toxic fumes.*

Pyridine (0.097 mL, 1.2 mmol) and phenacyl bromide (0.239 g, 1.2 mmol) were taken up in toluene (10 mL), and the mixture was stirred at room temperature (rt) for 1 h. To this mixture methyl thiocyanate (0.074 g, 1.0 mmol) and potassium carbonate (0.28 g, 2.0 mmol) were added, and the mixture was allowed to stir at reflux for 12 h. Upon completion, the toluene was removed under reduced pressure, then water was added, and the reaction mixture was extracted with dichloromethane (3 × 15 mL). The organic layer was dried over Na_2SO_4. Evaporation of the solvent followed by purification on silica gel (ethyl acetate−hexane, 1−9) afforded the pure **4**{*1,1,1*} as yellow solid (0.24 g, yield 78%). M.p 140 °C. IR (KBr) (ν_{max}/cm^{-1}): 1490, 1571, 1597, 3060. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 2.58 (3H, s, S-CH_3), 7.07−7.10 (1H, m), 7.52−7.57 (3H, m), 7.61−7.63 (1H, m), 7.68−7.72 (3H, m), 9.60 (1H, d, $^3J_{HH}$ = 6.9 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C (ppm): 15.32, 114.70, 116.24, 128.60, 128.63, 129.05, 129.07, 130.02, 132.05, 140.33, 148.55, 156.49, 186.05 (C═O). MS, *m*/*z* (%): 268 (M^+,100), 235 (67), 207 (33), 163 (26), 77 (44), 51 (23).

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Supporting Information Available. Experimental procedures, ^{1}H NMR and ^{13}C NMR spectra for compounds **4**, **6**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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