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Regiospecific Thermal C-Acylation of Imidazo [1,2-a] Pyridines via an N-Acylimidazolium Intermediate

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Abstract: Direct acylation of imidazo [1,2-a] pyridines in a sealed tube at 130°C and without catalyst gave various 3-acyl derivatives in satisfactory yields.

Keywords: acylation; imidazole; iminium salt; reaction under pressure

The most efficient method of synthesis of 3-acyl imidazo [1,2-a] pyridines **1** known to date is the alkylation of the corresponding N-pyridinyl formamidine **2** with a halomethyl ketone followed by cyclocondensation of the intermediate in the presence of a base (method a) [1]. Recently we described a novel method of preparation of similar compounds. It involves the α-bromination of the corresponding N-heteroaryl aminopropyl ketone **3** followed by cyclocondensation and thermal dehydrogenation of the dihydroimidazole intermediate **5** (method b) [2]. A third method formally might result from the direct acylation of imidazo [1,2-a] pyridines **6** (Scheme 1).

When compared to other substitution reactions involving imidazo [1,2-x] azines and carbonyl electrophiles such as formaldehyde [3,4], substitution systematically occurred at the 3 position of the imidazole ring. With another hard electrophile [5] such as an acyl chloride, in accordance with the HSAB theory [6], a similar behaviour should be expected. Such electrophilic substitutions are well reported on imidazoles and benzimidazoles [7]. However, to our knowledge, no work reports on the efficient direct acylation of imidazo [1,2-a] pyridines, or other imidazo [1,2-x] azines.

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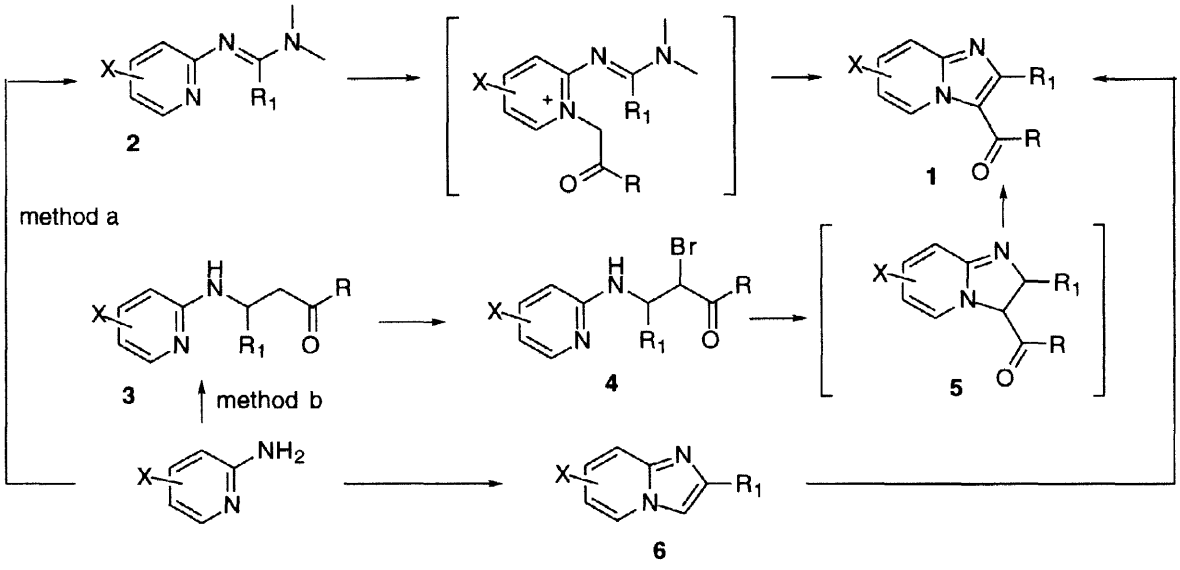
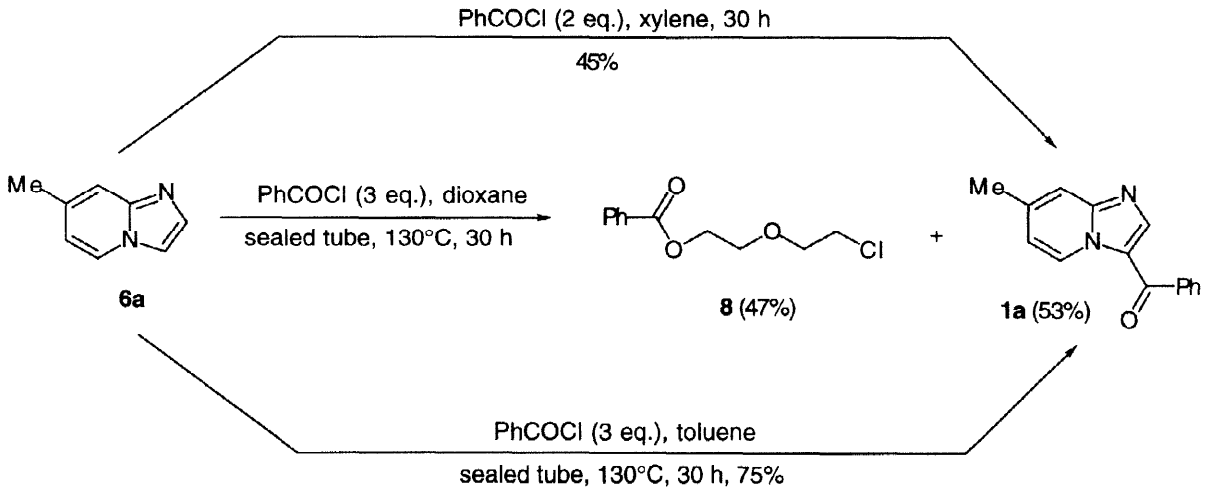


Scheme 1

We describe here the direct acylation of 7-methyl imidazo [1,2-a] pyridine **6a**. The scope and the limitation of this method in relation with the mechanism of action involved in this process is discussed.

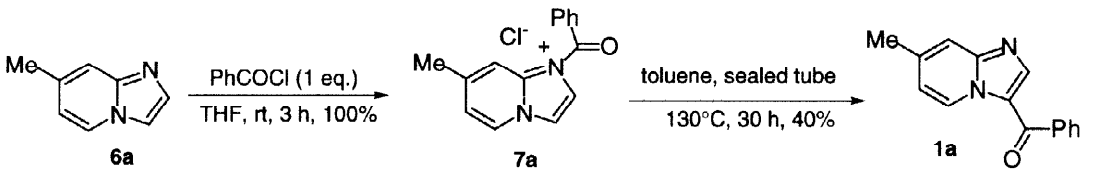
Reaction of **6a** with two equivalents of benzoyl chloride in refluxing xylene for thirty hours afforded the 3-benzoyl derivative **1a** in 45% yield. However, when reacting **6a** in a sealed tube at 130°C (external temperature), it gave unexpected results in dioxane, as in these conditions a significant amount of dioxane ring-opened derivative **8** was isolated (about 50%, based on benzoyl chloride, Scheme 2).



Scheme 2

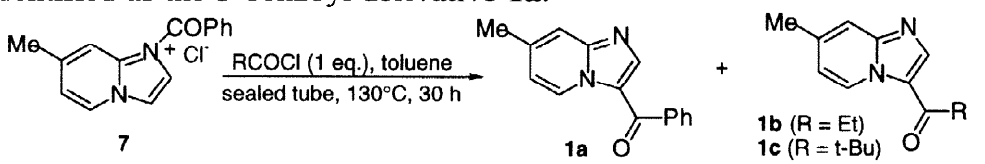
Finally in the presence of an excess (3 equivalents) of benzoyl chloride in toluene instead of xylene in similar experimental conditions as above, the expected benzoyl derivative **1a** was obtained in satisfactory yield (Table 1). Conducting the reaction at room temperature in THF for three hours afforded quantitatively the N-benzoyl imidazolic intermediate **7** as a

hygroscopic salt (Yield, 100%; mp 82°C; ^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.44 (3H, s, CH_3); 7.59-7.34 (7H, m, ArH+H6+H8); 8.98 (1H, s broad, H5); 9.75 (1H, s, H3); 10.79 (1H, s, H2). ^{13}C NMR ($CDCl_3$, 50 MHz) : δ 22.32; 113.49; 117.46; 122.44; 128.39; 129.06; 129.69; 131.63; 134.47; 139.22; 152.05; 165.34). Heating the salt in experimental conditions similar to those described above gave a mixture of nearly equimolecular amounts (about 40%) of the 3-benzoyl imidazo pyridine **1a** and the starting imidazo pyridine **6a** (Scheme 3).



Scheme 3

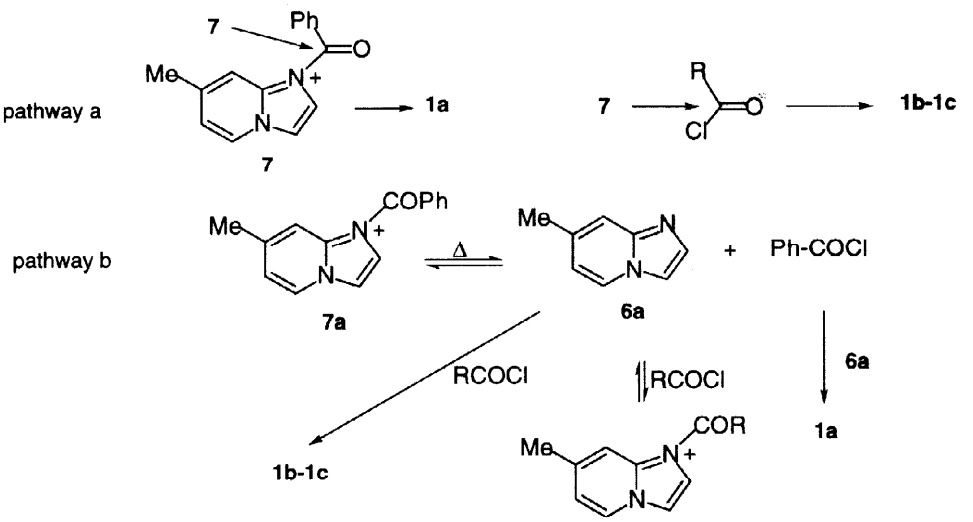
However, heating **7a** in a the sealed tube in the presence of one equivalent of acyl chloride afforded a mixture of 3-acyl derivatives (Table 1). The expected 3-acyl derivatives **1b** and **1c** were the major products (about 60%), but in each case the minor compound (~ 30%) was identified as the 3-benzoyl derivative **1a**.



Entry	electrophile	total yield (%) (**1a** + **1b** + **1c**)	yield % **1a**	**1b**	**1c**
1	none	40	40		
2	EtCOCl	80	25	55	
3	t-BuCOCl	89	30		59

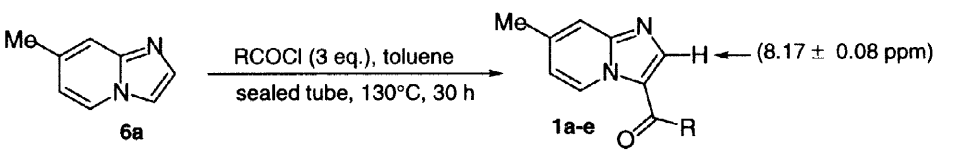
Table 1

The mechanism depicted in Scheme 4 accounts for the different observations reported here. The electrophilic reaction does not require any Lewis acid catalyst [8], or triethylamine mediated formation of an ylid intermediate [7]. The N-benzoyl imidazolium **7** may react with acyl chlorides to give the expected compounds **1b-1d** (R ≠ Ph). However the N-benzoyl iminium **7** remains a powerful electrophilic agent comparable to benzoyl chloride, and then might react with a second molecule to afford the N-benzoyl derivative **1a** (pathway a, see Table 1, entry 1). It is noteworthy that the pathway b involving an equilibrium betwen N-acyl iminiums **7** and the starting imidazo pyridine **6** could not be discorded. The reverse acylation reaction would provide **6a** as a more reactive species able to be C-acylated by either benzoyl or acyl chloride. However, when **7a** was reacted with three equivalents of acyl chloride, trans acylation did not occur at room temperature. In addition data in Table 1, entry 1, (total yield < 50%) are also in favour of pathway a. Thus the cristalline N-benzoyl iminium **7** could not be used systematically for further reactions with various acylating agents.



Scheme 4

The acylation reaction was also carried out in presence of three equivalents of acylating reagent in order to avoid the formation of mixtures of acyl derivatives (see Table 2).



electrophile	1	R	yield (%)	mp, °C
PhCOCl	**a**	Ph	75	134
EtCOCl	**b**	Et	70	110
t-BuCOCl	**c**	t-Bu	70	115
n-BuCOCl	**d**	n-Bu	78	80
MeCOCl	**e**	Me	78	109
Ac_2O	**e**	Me	58	

Table 2

In conclusion we have described here a very simple acylation reaction of a typical imidazo [1,2-a] pyridine using an excess of acylating agent in a sealed tube at 130°C. The process involves a first activation step through quantitative N-acylation. The reaction may be extended to other heterocycles, leading to various 3-acyl imidazo [1,2-x] azines.

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