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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. © 1998 Published by Elsevier Science Ltd. All rights reserved.

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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; ¹H NMR (CDCl₃, 200 MHz) : δ 2.44 (3H, s, CH₃); 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). ¹3C NMR (CDCl₃, 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).



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**.

M		Ph Me RCOCI (1 eq.), toluene sealed tube, 130°C, 30 h	Ha O Ha O Ha Ha O Ha		
Entry	electrophile	total yield (%)		yield %	
		<u>(1a + 1b + 1c)</u>	1a	1b	1c
1	none	40	40		
2	EtCOCI	80	25	55	
3	t-BuCOCI	89	30		59

Table

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** ($R \neq Ph$). 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.





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).

Ме		RCOCI (3 eq.), sealed tube, 1	Me toluene 30°C, 30 h	Me N N N N (8.17 ± 0.08 ppm)		
	6a electrophile	1	R	1a-e OR yield (%)	mp, °C	
	PhCOCI	а	Ph	75	134	
	EtCOCI	b	Et	70	110	
	t-BuCOCI	С	t-Bu	70	115	
	n-BuCOCI	ď	n-Bu	78	80	
	MeCOCI	e	Me	78	109	
	Ac ₂ O	e	^{Me} Table 2	58		

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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