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Selective O-Acylation of Aromatic Hydroxylamines by 2-Acylimidazolium and 2-Acylbenzimidazolium Salts

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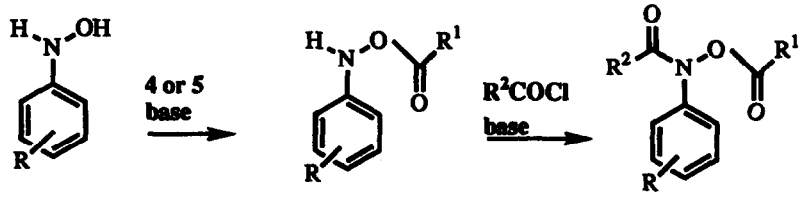
Abstract.— 2-Acyl 1,3-dimethylbenzimidazolium and 2-acyl 1,3-dimethylimidazolium salts react with N-aromatic hydroxylamines in the presence of base to give the O-acyl derivatives.

The process of cancer induction by aromatic amines **1** is thought to proceed by oxidation of its nitrogen atom followed by O-acetylation of the resulting hydroxylamines **2** to produce the unstable O-acyl derivatives **3**.[1] These are postulated to be responsible for the formation of the DNA adducts which cause the primary cancer lesion. As a part of a project to develop selective acylating agents for the **2** -> **3** transformation, we undertook a systematic study of potential acyl transfer agents that might show the desired selectivity. 2-Acylimidazolium (**4**) and 2-acylbenzimidazolium salts (**5**) were found to act as acylating agents towards various nucleophiles such as alcohols, phenols, amines and thiols[2-7]. When these salts were allowed to react with N-aryl hydroxylamines (ambident nucleophiles) it was found that exclusive O-acylation of the latter proceeded in good yields to afford the derivatives **3**, and the results are disclosed in the present letter. Thus **2** (R=H) (1 equiv) in dry CH_2Cl_2 on reaction (30 min) with 2-acetyl 1,3-dimethylbenzimidazolium† triflate **5a** (X=CF_3SO_3) or iodide (X = I) (1 equiv) in the presence of base (triethylamine or 1,4-diazabicyclo[2.2.2]octane) (1 equiv) at room temperature provided compound **3** (R=H, R^1=CH_3) identical with an authentic sample[8] in 75% yield. In the absence of base no reaction is observed. Since these type of compounds are unstable, **3** was further characterized as the more stable crystalline N-4-nitrobenzoyl derivative[8] **6** (R=H, R^1=CH_3, R^2= 4-$NO_2C_6H_4$). The results obtained with other aromatic hydroxylamines and 2-acylimidazolium salts are summarized in the Table. With the exception of N-4-methylphenyl hydroxylamine (entry *9*) which gives rise to rearranged products[8] owing to the instability of the initially formed O-acyl derivative, all other hydroxylamines react to afford the corresponding N-acyloxy anilines. Though 2-acylimidazolium salts are not normal biological products, they nevertheless may be formed in certain pathological conditions. Such is the case in diabetes, where the presence of high concentrations of glucose leads to nonenzymatic condensation with amino groups or side chains of lysine residues to form Schiff bases. With time these undergo Amidori rearrangement to fructosamine, and when two such units on different peptide chains meet, they can react to crosslink the two chains, leading to the furanyl-furoyl-imidazolium structures of type **7**.[11] When 2-furoyl 1,3-dimethylimidazolium triflate **4c**

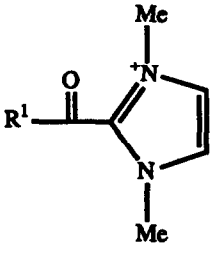
Table.— N,O-Diacyl N-aryl hydroxylamines (6)

Entry	Acylating Agent	6 R	6 R^1	6 R^2	Yield,%[a]	mp°C (mp° C Lit.)	IR, cm^{-1} (KBr)
1	4a	H	CH_3	C_6H_5	86	145-7 (146.5-8)[8]	1800, 1680
2	4a	4-Br	CH_3	4-$NO_2C_6H_4$	70	161-4 (162-3)[8]	1780, 1680
3	4a	3-Me	CH_3	4-$NO_2C_6H_4$	85	146-8	1800, 1680
4	4a	4-NO_2	CH_3	4-$NO_2C_6H_4$	67	137-9	1808, 1698
5	5a	H	CH_3	C_6H_5	73 (75[b])	51-5	1790, 1670
6	5a	H	CH_3	4-$NO_2C_6H_4$	75	146-8 (146.5-8)[8]	1800, 1680
7	5a	4-Br	CH_3	4-$NO_2C_6H_4$	69	161-4 (162-3)[8]	1780, 1680
8	5a	3-Me	CH_3	4-$NO_2C_6H_4$	50	143-5	1800, 1680
9	5a	4-Me	CH_3	-	0[c]	-	-
10	5b	H	C_6H_5	4-$NO_2C_6H_4$	63	135-9 (136-8)[9]	1775, 1690
11	5b	4-Br	C_6H_5	4-$NO_2C_6H_4$	24	114-5	1770, 1675
12	5b	3-Me	C_6H_5	4-$NO_2C_6H_4$	31	134-5	1790, 1685
13	5b	4-Cl	C_6H_5	4-$NO_2C_6H_4$	30	120-2	1770, 1690
14	5b	4-NO_2	C_6H_5	4-$NO_2C_6H_4$	52	145-7	1780, 1695
15	4c	H	2'-furanyl	4-$NO_2C_6H_4$	89	157-160	1752, 1684
16	4c	3-Me	2'-furanyl	4-$NO_2C_6H_4$	84	112-114	1772, 1700
17	4c	4-Br	2'-furanyl	4-$NO_2C_6H_4$	79	57- 60	1776, 1688
18	4c	3-Br	2'-furanyl	4-$NO_2C_6H_4$	84	50-50.5	1772, 1688

[a] Represent yields of 6 purified by chromatography and/or crystallisation. [b] Yield of 3 (R = H, R^1 = CH_3) by ^1H NMR. [c] Extensive decomposition of 3 (R = 4-CH_3, R^1 = CH_3), as previously recorded.[8]

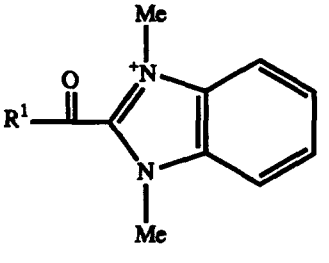


2 3 6



X⁻

4



X⁻

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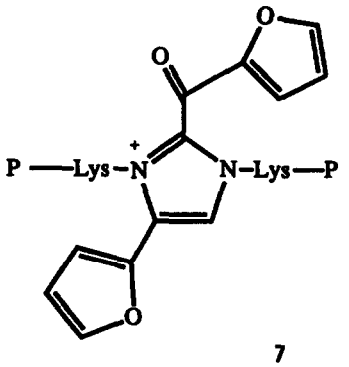
a: $R^1 = CH_3$
b: $R^1 = C_6H_5$
c: R^1 = 2'-furanyl



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P = Protein chain

Lys = Lysine

(X=CF_3SO_3), modelled upon **7**, reacted with several N-aryl hydroxylamine **2** exclusive O-acylation was also observed to occur in high yield, and the products were characterised as the corresponding acyl derivatives **6** (entries *15* to *18*).

The present results are reminiscent of the selective O-acylation which occurs when acyl cyanides[8-10] or 2-acyl N-methylthiazolium triflates[12] react with aromatic hydroxylamines.

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References and Notes

1 F. A. Beland and M. C. Poirier, in "The Phatobiology of Neoplasia", A. E. Sirica (Ed.), Plenum Pu., 1989, p. 57.
2 S. Ohta, S. Hayakawa, H. Moriwaki, S. Tsuboi and M. Okamoto, *Heterocycles*, **1985**, *23*, 1759.
3 (a) J. Glowczyk and B. Serafin, *Pol. J. Chem.*, **1984**, *58*, 149; (b) J. Glowczyk and B. Serafin, *Pol. J. Chem.*, **1978**, *52*, 1467.
4 B. Serafin and J. Glowczyk, *Rocz. Chem.*, **1976**, *50*, 1211.
5 R. C. F. Jones and J. R. Nichols, *Tetrahedron Lett.*, **1990**, 1771.
6 T. C. Owen and A. Richards, *J. Am. Chem. Soc.*, **1987**, *109*, 2520.
7 For an interesting lactonisation procedure *cf.* D. H. Davies, J. Hall and E. H. Smith, *J. Chem. Soc. Perkin Trans. 1*, **1991**, 2691.
8 A. M. Lobo, M. M. Marques, S. Prabhakar and H. S. Rzepa, *J. Org. Chem.*, **1987**, *52*, 2925. The derivatives **6** (R=H, R^1=CH_3, R^2= 4-$NO_2C_6H_4$) were prepared by dissolving **3** (R=H, R^1=CH_3) (1 equiv) in dry THF and allowing it to react at -40° to -50° C with 4-nitrobenzoyl chloride (2 equiv) in the presence of NaH (3 equiv) or Et_3N (1 equiv), followed by careful acidification of the reaction mixture with acetic acid and chromatographic purification (SiO_2, MeOH:CH_2Cl_2 , 2%).
9 S. Prabhakar, A. M. Lobo and M. M. Marques, *Tetrahedron Lett.*, **1982**, 1391
10 A. M. Lobo, M. M. Marques, S. Prabhakar and H. S. Rzepa, *J. Chem. Soc., Chem. Commun.*, **1985**, 1113.
11 S. C. Stinson, Chem. Eng. News, September 30, **1991**, 35.
12 L. M. Ferreira, A. M. Lobo, S. Prabhakar, M. J. M. Curto, H. S. Rzepa and M. Y. Yi, *J. Chem. Soc., Chem. Commun.*,, **1991**, 1127.
13 G. H. H. Cheeseman, *J. Chem. Soc.*, **1964**, 4645.

† All new compounds gave spectral data (i.r., n.m.r., m.s.) in accord with the assigned structure, and satisfactory microanalysis or accurate mass measurement. Compound **5a** was easily obtained by alkylation of 2-acetyl 1-methylbenzimidazole[13] with MeI (X = I , mp 185-8 °C, lit.[4] mp 185-8 °C) or with $CF_3SO_3CH_3$. Selected data: **4a** (X = CF_3SO_3) : m.p. 75-78 °C; ν_{max} (KBr) 1715 cm^{-1}; δ_H (DMSO-d_6) 2.72 (3H, s, CH_3C), 4.05 (6H, s, 2 x N-CH_3), and 7.87 (2H, s, C_4-H and C_5-H); **5a** (X = CF_3SO_3) : m.p.77-80 °C; ν_{max} (KBr) 1700 cm^{-1} ; δ_H (DMSO-d_6) 2.92 (3H, s, CH_3C), 4.23 (6H, s, 2 x N-CH_3), and 7.83 (2H, m , Ar-H), 8.19 (2H, m, Ar-H); **4c** (X = CF_3SO_3) : m.p. 83-85 °C; ν_{max} (KBr) 1640 cm^{-1} ; δ_H (CD_2Cl_2) 3.94 (6H, s, 2 x N-CH_3), 6.86 (1H, dd, J_1 3.8 Hz, J_2 1.7 Hz, C_4'-H, furan), 7.70 (2H, s, C_4-H and C_5-H), 7.79 (1H, dd, J_1 3.8 Hz, J_2 0.6 Hz, C_5'-H, furan), 7.97 (1H, dd, J_1 1.7 Hz, J_2 0.6 Hz, C_3'-H, furan).

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