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AMIDINOETHYLATION—A NEW REACTION—IV

THE AMIDINOETHYLATION OF ALCOHOLS: A FACILE SYNTHESIS OF 3-ALKOXY-N,N'-SUBSTITUTED-PROPANAMIDINES[1]

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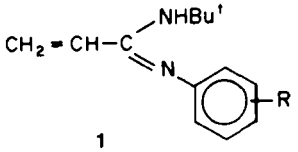
Abstract—The amidinoethylation of alcohols takes place by the addition of sodium alkoxides **2** (R^1 = Me, Et) to the C=C double bond of a variety of N,N'-substituted-propenamidines **1** (Method A). This illustrates the activation of the C=C double bond by the conjugated amidine function and provides a new class of Michael acceptors for alcohols. However, this activation is poorer than with other nucleophiles or Michael acceptors. The amidinoethylation makes available 3-alkoxy-N,N'-substituted-amidines not easily accessible by other classical methods. However, it is demonstrated that the general N,N'-substituted-amidine synthesis via the nitrilium salts can also apply to nitrile compounds having an alkoxygroup present on the molecule (method B). Since the cyanoethylation of alcohols (**4**) is a very fast and facile reaction the method B is the preferred strategy for the synthesis of 3-alkoxy-N,N'-substituted-propanamidines **3**.

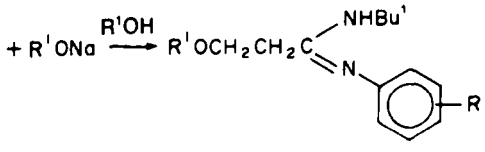
We have reported earlier the amidinoethylation of thiols,[2] compounds with active methylene[3] and amines[1] carried out by their Michael addition to N,N'-substituted-propenamidines. The study of this novel reaction is now extended to the addition of alcohols as nucleophiles. Their addition to activated olefins is well known[4-12] and reviewed.[13] It is usually base catalysed and the active species is the alkoxide, the rate determining step being its addition to the Michael acceptor. An acid catalysed addition has also been reported.[8,9]

The addition of alcohols to the C=C double bond of N,N'-substituted-propenamidines **1** has been investigated under various conditions and the highest yields in 3-alkoxypropanamidines **3** was obtained using sodium alkoxide. As models of vinylamidines **1** we have chosen the easily accessible N-*t*-butylpropenamidine derivatives recently described.[16] However, this reaction should work just as well whatever be the N-substituents (e.g. isopropyl).[15]

Method A



1

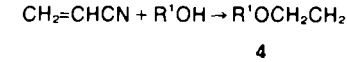


2 **3**

Although alcohols are much less acidic and nucleophilic than thiols attempts have been made to induce the addition of alcohol to **1** hoping an autocatalytic effect similar to what was previously obtained with thiols.[2] However, no reaction leading to **3** was observed, even after one week. The same negative result was obtained when the hydrochloride of the amidine **1** was heated during 1 week in methanol. But when the amidine **1** was heated in the presence of 1 equivalent of sodium alkoxide, an addition took place yielding **3** in 70% yield. It was reported earlier that the rate of methoxide addition to activated olefins was increased by addition of aprotic polar or non polar solvents.[4,6,7] Thus when **1a** and **2a** were heated in a 1:1 mixture of methanol:1,2-dimethoxyethane; an accelerating effect was observed and **3** was formed in 84% yield after 36 hr, whereas if DMF was used instead of 1,2-dimethoxyethane, an 86% yield was obtained after 24 hr. These experimental conditions were used to prepare a series of 3-alkoxy-N,N'-substituted propanamidines **3a–e** in good yields starting from 4 differently N,N'-substituted-propenamidines **1** and sodium methoxide or ethoxide (Table 1, Method A. column 5).

N,N'-substituted-amidines with an ether–oxide chain are not easily accessible. Thus, we achieved the preparation of **3** using another route (method B): (a) The cyanoethylation of alcohol published earlier[10] yielded 86% and 83% of 3-methoxy- and 3-ethoxypropanenitrile **4** (R^1 = Me and Et). (b) Formation of the amidine **3** via the nitrilium salts.[15,16] The alkoxy-group did not prevent the formation of the nitrilium salt **5** (*cf* with the previous report where a 3-amino-function was present instead[1]) and the amidine **3** was isolated in good yields (see Table 1, method B, column 8).

Method B



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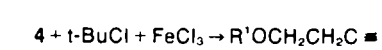

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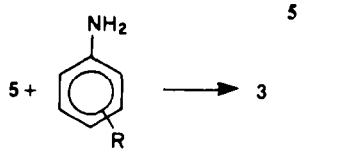

All 3-alkoxy-N,N'-substituted-propanamidines **3a–e** described are new. Their structure established by iden-

Table 1. The 3-alkoxy-N,N'-substituted-propanamidines 3

Product	R^1	R	Yield %[a] in 1[16]	Yield % in 3 Method A	Overal yield %[a] Method A	Yield %[a] in 4[10]	Yield % in 3 Method B	Overal yield %[a] Method B	B.P.°C/ Torr 3	M^+ Molecular Formula	HCl salt m.p.°C solvent
3a	CH_3	2,6-diCl	66	86	58.5	86	79	68	150/1	303 $C_{14}H_{20}N_2OCl_2$	215[b] $CHCl_3$/EtOH/Et_2O
3b	C_2H_5	2-H_3C	75	70	52.5	83	68	56.5	135/1	262 $C_{16}H_{26}N_2O$	183 $CHCl_3$/Et_2O
3c	C_2H_5	2,6-diCl	66	73	48	83	69	57	152/1,5	317 $C_{15}H_{22}N_2OCl_2$	208[c] $CHCl_3$/EtOH/Et_2O
3d	CH_3	2-Cl	76	75	57	86	70	60	126/1,2	268 $C_{14}H_{21}N_2OCl$	192 $CHCl_3$/Et_2O
3e	CH_3	3-F_3C	62	68	42	86	-	-	158/1	302 $C_{15}H_{21}N_2OF_3$	156 $CHCl_3/Et_2O$

(a) from propenenitrile (b) found : C49, 32; H6,12; N8,09; Cl31,58; Calc.for $C_{14}H_{21}N_2OCl_3$; C49,50; H6,23; N8,25; Cl31,31; (c) found : C50,75; H6,41; N7,80; Calc.for $C_{15}H_{23}N_2OCl_3$; C50,93; H6,55; N7,92.

Table 2. IR spectra for compounds **3a–e**

Product n°	ν (cm^{-1}) ; film [a]
3a	3380 (m,NH); 2820 (w,-OCH_3); 1640 (vs, C=N); 1580 (C=C_{ar});
3b	3390 (m,NH); 2815 (-OCH_3); 1640 (vs, C=N); 1595 (C=C_{ar});
3c	3380 (m,NH); 1640 (vs, C=N); 1600 (s, C=C_{ar});
3d	3390 (m,NH); 1645 (vs, C=N); 1585 (s, C=C_{ar});
3e	3380 (m,NH); 1635 (vs, C=N); 1600 (s, C=C_{ar}); 1315, 1165, 1120 (vs, CF_3)

(a) vs = very strong; s = strong; m = medium; w = weak

Table 3. ^{1}H-NMR data for compounds **3a–e**

Product n°	δ (ppm) in $CDCl_3$ [a]
3a	7,3-6,5 (3m,Ar<u>H</u>); 5,55 (1NH); 3,4 (2t,-OC<u>H</u>$_2$-CH_3); 3,3 (3s,-OCH_3); 2,1(2t,-CH_2-C(=N-)-N; 1,45(9s, C_4H_9-t);
3b	7,2-6,4(4m,Ar<u>H</u>); 5,2(1NH); 3,6-3,2(4m,-C<u>H</u>$_2$-O-C<u>H</u>$_2$-); 2,2(2t,-CH_2-C(=N-)-N-;2,05(3s,ArC<u>H</u>$_3$); 1,4(9s,C_4H_9-t); 1,2(3t,C<u>H</u>$_3$-CH_2-O-);
3c	7,4-6,6(3m,Ar<u>H</u>); 5,85(1NH);3,7-3,3(4m,-C<u>H</u>$_2$-O-C<u>H</u>$_2$-); 2,2(2t,-CH_2-C(=N-)-N-; 1,5(9s,C_4H_9-t); 1,2(3t,C<u>H</u>$_3$-CH_2-O-);
3d	7,5-6,6(4m,Ar<u>H</u>); 5,3(NH); 3,4(2t,-O-CH_2); 3,25(3s,-O-CH_3); 2,18(2t,-CH_2-C(=N-)-N-;1,4(9s,C_4H_9-t);
3e	7,5-6,7(4m,Ar<u>H</u>); 5,3(1NH); 3,45(2t,-OC<u>H</u>$_2$); 3,3(3s,-OC<u>H</u>$_3$); 2,35(2t,CH_2-C(=N-)-N-; 1,4(9s,C_4H_9-t);

(a) s = singlet; d = doublet; t = triplet; q = quadruplet, h = heptuplet; m = multiplet.

tity of the IR spectra of **3** isolated from both methods; all display the characteristic very strong $\nu_{C=N}$ band of the amidine function at 1635–1645 cm^{-1}. Some other IR bands are also tabulated (Table 2). The ^{1}H-NMR spectra have been recorded and all signals attributed (Table 3). The molecular formulae have been confirmed by mass spectrometry and the elementary analysis of **3a,c** (Table 1).

In conclusion, the amidinoethylation of alcohols by the addition of sodium alkoxides to the C=C double bond of propenamidines **1** illustrates the activation by the conjugated amidine function thus providing a new class of Michael acceptors for alcohols. However, under the strongly basic experimental conditions used here, this activation is poorer than with other nucleophiles such as thiols,[2] amines[1] and compounds with an active methylene[3] or compared to other Michael acceptors such as propenenitrile.[10] It has been also shown that the presence of an alkoxy function on a nitrile compound does not prevent the efficiency of the amidine synthesis via the nitrilium salts **5** (*cf* the yields in Table 1, column 4 and 8). Taking into account the overall yield for the synthesis of **3** from propenenitrile, the method B gives slightly better results than the method A (Table A, *cf* the figures of column 6 and 9). Moreover, since the cyanoethylation of alcohols is a very facile reaction,[10] the method B is the preferred strategy for the synthesis of 3-alkoxy-N,N'-substituted-propanamidines **3** and we may anticipate that it is as well applicable to the synthesis of 3-aryloxy-N,N'-substituted-propanamidines. The compounds **3** have been screened for their pharmacological activity.[17]

EXPERIMENTAL

M.ps were determined on a Kofler hot-stage apparatus. B.ps are uncorrected IR spectra were measured on a Perkin–Elmer 177 spectrophotometer as KBr pellets or when liquid on film over NaCl plates. ^{1}H-NMR spectra were recorded on a Varian T-60 or Jeol JNM-MH 100 instrument using TMS as internal standard. Mass spectra were recorded on a Hitachi Perkin–Elmer RMU-60 instrument. The synthesis of N,N'-substituted-propenamidines **1** has been reported earlier.[15,16]

3-*Alkoxy*-N,N'-*substituted-propanamidines* **3a–e**

Method A: *Amidinoethylation of methanol.* To 20 ml abs. MeOH 0.47 g (0.02 mol) of Na, then a soln of 5.42 g (0.02 mol) of **1a**[16] in 20 ml anhyd DMF was added. The mixture was heated under reflux during 24 hr, then cooled and diluted with 50 ml water. It was then extracted with $CHCl_3$ and the organic phase washed 3 times with 20 ml water, dried over $MgSO_4$ and evaporated to dryness.

The residue was distilled with a 15 cm Vigreux column and the fraction b.p. 150°/1 Torr was pure (glc on Carbowax 20 M, Isotherm 180°) 3-methoxypropanamidine **3a**: 5.01 g (yield: 86%). The amidinoethylation of EtOH was carried out under similar conditions with abs EtOH instead of abs MeOH. All data are summarised on Tables 1–3.

Method B: *3-methoxypropanamidine* **3a** *from 3-methoxypropanenitrile* **4** (R^1 = Me). Compound **4** (R^1 = Me and Et) was prepared according to the updated method[10] in 86 and 83% yields (respectively). To a −30° cooled and magnetically stirred suspension of 5.7 g anhyd $FeCl_3$ (0.035 mol) in 20 ml anhyd Ch_2Cl_2, 3 g 3-methoxypropanenitrile (0.0351 mol) was added. The mixture turned dark red while the $FeCl_3$ was dissolving. It was then cooled to −40° and 3.9 ml *t*-BuCl (0.0351 mol) was added. The temp. was allowed to rise to −5° while the nitrilium salt formed. The mixture was cooled to −60° and 5.7 g (0.0351 mol) 2,6-dichloraniline in 10 ml $CHCl_2$ was added. The mixture was kept at room temp. during 15 min and stirring continued. Then 30% cooled (−15°) NaOH aq (0.156 mol) was poured into the mixture which was then extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$, filtered and concentrated to dryness. The oily residue was distilled with a horizontal distillation apparatus (Kugelrohr, Aldrich) giving 7.95 g of **3a** whose IR spectrum was superimposable with the one obtained by method A. The other amidines **3b–d** were similarly prepared and all data are summarized on Tables 1, 2 and 3.

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