Amidinoethylation - A New Reaction; I. The Amidinoethylation of Thiols; A Facile Synthesis of 3-Alkylthio- and 3-Arylthiopropanamidines[1]

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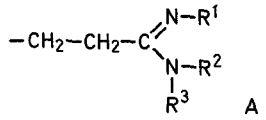
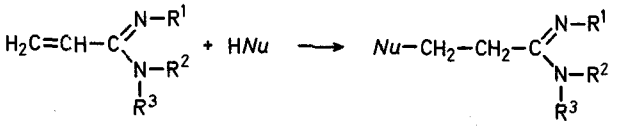
N-Substituted propenamidines were first prepared a few years ago[2,3]. Since then a series of new N^1-*t*-butyl-N^2-substituted-propenamidines **1** have become available[1]. We now describe the use of compounds **1** as activated carbon-carbon double bond systems in reactions with compounds possessing a labile hydrogen atom (H*Nu*) to give products containing the amidinoethyl group A.

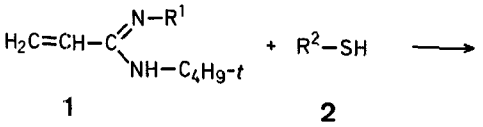


A

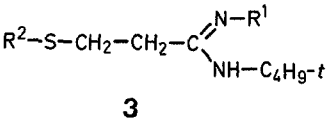
This new process has been termed the amidinoethylation reaction and has some resemblance to the Michael addition[4].



The Michael reaction (with *C*-nucleophiles) usually occurs in the presence of a basic catalyst. Therefore, owing to the strongly basic nature of the amidine function[5], an autocatalytic effect could be expected for the amidinoethylation reaction. This effect has been observed in the addition of thiols **2** ($R^2 = n\text{-}C_4H_9$, C_6H_5) to propenamidines **1**.



1 **2**



3

The analogous addition of thiols to the carbon-carbon double bonds of propenenitriles, propenoic acid, propenoates, or acrolein requires the presence of a basic catalyst such as

Table 1. *3-Alkylthio- and 3-Arylthio-N'-t-butylpropanamidines* **3**

Product No.	R^1	R^2	Yield[a] [%]	m.p. (solvent) or b.p./torr	Molecular formula[b]
3a	4-C_2H_5OOC—C_6H_4	C_6H_5	93	103–104 °C (C_2H_5OH)	$C_{22}H_{28}N_2O_2S$ (385.5)
3b	2,6-di-Cl—C_6H_3	C_6H_5	98[c]	156–157 °C ($CHCl_3/C_2H_5OH$/ether)	$C_{19}H_{23}Cl_3N_2S$ (418.8)
3c	2-NC—C_6H_4	C_6H_5	92	65–66 °C (CH_3OH)	$C_{20}H_{23}N_3S$ (338.5)
3d	4-O_2N—C_6H_4	C_6H_5	90	67–68 °C (CH_3OH)	$C_{19}H_{23}N_3O_2S$ (358.5)
3e	2-Cl—C_6H_4	C_6H_5	98[c]	144–145 °C ($CHCl_3/C_2H_5OH$/ether)	$C_{19}H_{24}Cl_2N_2S$ (383.4)
3f	2-H_3COOC—C_6H_4	C_6H_5	90	83–84 °C (C_2H_5OH)	$C_{21}H_{26}N_2O_2S$ (371.5)
3g	4-C_2H_5OOC—C_6H_4	n-C_4H_9	90	69–70 °C (C_2H_5OH)	$C_{20}H_{32}N_2O_2S$ (364.5)
3h	4-O_2N—C_6H_4	n-C_4H_9	96	60–61 °C (C_2H_5OH)	$C_{17}H_{27}N_3O_2S$ (337.5)
3i	2-NC—C_6H_4	n-C_4H_9	89	37–38 °C (C_2H_5OH)	$C_{18}H_{27}N_3S$ (317.5)

[a] Yield of recrystallised product.

[b] The microanalyses were in satisfactory agreement with the calculated values (C ±0.3, H ±0.2, N ±0.4).

[c] Isolated and characterised as hydrochloride.

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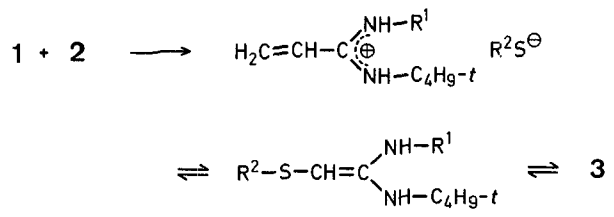
Table 2. I.R. and ^{1}H-N.M.R. Data for Compounds **3a-i**

Product	I.R. (KBr)[a] ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
3a	3400 (s, NH); 2960 (w, C—H_{arom}); 1960 (s, C=O); 1640 (C=N); 1590 (C=C); 810 (w, C—S)	7.9–6.5 (m, 9H_{arom}); 4.4 (1H, NH); 4.35 (2H, OCH_2); 2.85 (2H, SCH_2); 2.3 [2H, CH_2—C(=NR^1)—NHR^2]; 1.7–1.3 (12H); 1.35 (9H, t-C_4H_9)[b]
3b	2980 (w, C—H_{arom}); 1640 (vs, C=N); 1580 (vs, C=C); 840 (w, C—S)	7.6–6.5 (m, 8H_{arom}); 4.55 (1H, NH); 2.9 (2H, SCH_2); 2.1 [2H, CH_2—C(=NR^1)—NHR^2]; 1.4 (9H, t-C_4H_9)[b]
3c	3400 (s, NH); 3030 (w, C—H_{arom}); 2210 (s, C≡N); 1630 (vs, C=N); 1590 (C=C); 820 (w, C—S)	7.8–6.7 (m, 9H_{arom}); 4.8 (1H, NH); 3.0 (2H, SCH_2); 2.5 [2H, CH_2—C(=NR^1)—NHR^2]; 1.5 (9H, t-C_4H_9)
3d	3390 (s, NH); 2990 (w, C—H_{arom}); 1620 (vs, C=N); 1580 (vs, C=C); 1540 (vs, as-NO_2); 1320 (vs, sym-NO_2); 810 (w, C—S)	8.3–6.5 (m, 9H_{arom}); 4.6 (1H, NH); 2.9 (2H, SCH_2); 2.4 [2H, CH_2—C(=NR^1)—NHR^2]; 1.4 (9H, t-C_4H_9)
3e	2980 (w, C—H_{arom}); 1630 (vs, C=N); 1580 (w, C=C); 840 (w, C—S)	7.5–6.7 (m, 9H_{arom}); 3.3–2.6 [5H, NH, SCH_2, CH_2—C(=NR^1)—NHR^2]
3f	3400 (s, NH); 3060 (w, C—H_{arom}); 1720 (vs, C=O); 1640 (vs, C=N); 1595 (w, C=C); 830 (w, C—S)	8.0–6.5 (m, 9H_{arom}); 4.4 (1H, NH); 3.8 (3H, OCH_3); 2.9 (2H, SCH_2); 2.4 [2H, CH_2—C(=NR^1)—NHR^2]; 1.4 (9H, t-C_4H_9)
3g	3400 (s, NH); 2980 (w, C—H_{arom}); 1695 (vs, C=O); 1640 (vs, C=N); 1590 (vs, C=C); 820 (w, C—S)	8.1–6.6 (m, 4H_{arom}); 4.6 (1H, NH); 4.35 (2H, OCH_2); 2.7–2.1 [6H, SCH_2, CH_2—C(=NR^1)—NHR^2]; 1.7–1.1 (16H); 1.4 (9H, t-C_4H_9); 0.9 [3H, H_3C—$(CH_2)_3$—S]
3h	3410 (s, NH); 2980 (w, C—H_{arom}); 1630 (s, C=N); 1580 (s, C=C); 1520 (s, as-NO_2); 1320 (vs, sym-NO_2); 810 (w, C—S)	8.3–6.7 (m, 4H_{arom}); 4.9 (1H, NH); 2.8–2.2 [6H, SCH_2, CH_2—C(=NR^1)—NHR^2]; 1.5 (9H, t-C_4H_9); 1.5–1.2 (13H); 0.9 [3H, H_3C—$(CH_2)_3$—S]
3i	3400 (s, NH); 2980 (w, C—H_{arom}); 2230 (m, C≡N); 1630 (s, C=N); 1590 (m, C=C); 825 (w, C—S)	7.6–6.6 (m, 4H_{arom}); 4.95 (1H, NH); 2.9–2.1 [6H, SCH_2, CH_2—C(NR^1)—NHR^2]; 1.6–1.2 (13H); 1.5 (9H, t-C_4H_9); 0.9 [3H, H_3C—$(CH_2)_3$—S]

[a] vs = very strong; s = strong; m = medium; w = weak.
[b] DMSO-d_6 solution.

sodium methoxide or preferably benzyltrimethylammonium hydroxide for good yields of the product[6]. The present reaction, however, occurs on mixing equimolar amounts of **1** and **2** at room temperature. The reaction is exothermic and practically quantitative yields of **3** can be isolated (usually by crystallisation) after 15–60 min (Table 1). The progress of the reaction can be monitored by the disappearance of the vinyl—CH bands at ν = 930 and 980 cm^{-1} in the I.R. spectra.

The autocatalytic effect in this reaction can be rationalised by assuming the initial formation of an amidinium thiolate, as shown below, which is a better nucleophile than the thiol.



An alternative preparation of compounds **3** with functional groups in the 3-position would be difficult or proceed only in low yields depending on the nature of the functional group[7]. As an example, the yield for cyanoethylation of thiols lies in the range 52–97% depending on the catalyst[6]. The transformation of a nitrile into an amidine proceeds in lower yields when a heteroatom is in the 3-position.

The structures of all new compounds **3** prepared were confirmed by microanalysis, I.R., and ^{1}H-N.M.R. spectroscopy (see Tables).

3-Alkylthio and 3-Arylthio-N^1-t-butylpropanamidines 3; General Procedure:

The thiol **2** (0.011 mol) is added to the N'-t-butylpropenamidine **1** (0.01 mol) neat or in ethanol (15 ml) at room temperature. The temperature of the reaction mixture rises to ~60 °C. The mixture is allowed to cool to room temperature and after 1 h chloroform (50 ml) is added. The mixture is washed twice with 5% aqueous sodium hydroxide solution (2 × 50 ml) and twice with water. The organic phase is separated, dried with magnesium sulphate, and evaporated. The residue **3** is recrystallised from an appropriate solvent (see Table 1) or, if liquid, converted to the hydrochloride for characterisation.

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