A FACILE, CONVENIENT AND SELECTIVE HOMOLYTIC CARBAMOYLATION OF HETEROAROMATIC BASES

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Abstract - The oxidative decarboxylation of monoamides of oxalic acid provides carbamoyl radicals, which are useful for the selective arbamoylation of protonated heteroaromatic bases; this reaction represents the first general and selective method for the *N*-alkyl or *N*-arylcarbamoylation of heteroaromatic bases. Compared to alkoxycarbonylation, this reaction is much more effective and selective, owing to more favourable polar and enthalpic effects. The importance of the steric effects is also emphasized.

The direct selective introduction of the carbamoyl group ($CONH_2$) into heteroaromatic bases by radical reactions (eqs. 1 and 2) has a wide synthetic interest and, due to experimental simplicity, cheap reagents, high yields and selectivity, it has all the features of a useful reaction.[1]

$$\text{Het-H} + HCONH_2 + H_2O_2 \xrightarrow{\text{Fe(III)}} \text{Het-}CONH_2 + 2\,H_2O \qquad (1)$$

$$\text{Het-H} + HCONH_2 + NH_2OSO_3H \xrightarrow{\text{Fe(III)}} \text{Het-}CONH_2 + NH_4HSO_4 \qquad (2)$$

Het-H = Heteroaromatic base

Such reactions are much less effective with *N*-alkyl- and *N*-arylformamides because radicals $\cdot OH$ and $\cdot^{+}NH_3$, formed as intermediates in reactions (1) and (2) respectively, are very reactive and unselective species, so that they undergo both hydrogen abstraction from all available C-H bonds and addition to the different available positions on the aromatic ring, thus leading to complex mixtures of reaction products. Moreover, the use of formamide as the solvent contributes to the effectiveness and selectivity of reactions (1) and (2); this is much less convenient with more complex *N*-substituted formamides.

We now report a new and selective general procedure for the free-radical carbamoylation of heteroaromatic bases by oxidative decarboxylation of oxalic acid monoamides (eq. 3).

$$R_2N\text{-}CO\text{-}COOH \xrightarrow{-e} R_2N\text{-}\dot{C}O + CO_2 + H^+ \qquad (3)$$

Monoamides of oxalic acid were easily obtained from the chloride of oxalic acid monomethyl ester (eq. 4) or from the corresponding diester (eq. 5).

$$MeOCOCOCl + R_2NH \longrightarrow MeOCOCONR_2 \xrightarrow{OH^-} HOOC\text{-}CONR_2 \qquad (4)$$

$$MeOCOCOOMe + R_2NH \longrightarrow MeOCOCONR_2 \xrightarrow{OH^-} HOOC\text{-}CONR_2 \qquad (5)$$

Though several oxidants (Ce(IV), Co(III), Mn(III), Pb(IV) salts, Barton esters, iodoso carboxylates) proved to be successful for generating carbamoyl radicals from the monoamides of oxalic acid, silver-catalyzed persulfate was chosen as the most effective, simple, cheap and selective method available for the carbamoylation of heteroaromatic bases (eq. 6).

$$Het\text{-}H + R_2NCO\text{-}COOH + S_2O_8^{=} \xrightarrow{Ag^+} Het\text{-}CONR_2 + CO_2 + 2\ HSO_4^- \qquad (6)$$

The reaction was carried out in a two-phase system: an aqueous phase containing sodium persulfate, the protonated base and the catalyst ($AgNO_3$), and a CH_2Cl_2 layer which dissolves the monoamide of oxalic acid. Operating in a two-phase system is particularly effective to increase yields in monosubstitution, as shown by the results of Table 1. The carbamoyl radicals have a clear-cut nucleophilic character and the reaction is particularly sensitive to polar effects,[1,2] so that the introduction of a carbamoyl group significantly increases the reactivity of the heterocyclic ring, leading to polysubstitution on rings bearing more than one free position of high nucleophilic reactivity (e.g. on quinoline, quinoxaline, 4-cyanopyridine). On the other hand the introduction of a carbamoyl group reduces the basicity and therefore the protonation of the heteroaromatic compound: the unprotonated monosubstituted product is therefore extracted by CH_2Cl_2 during the reaction, thus preventing further substitution, which would take place in the aqueous phase.

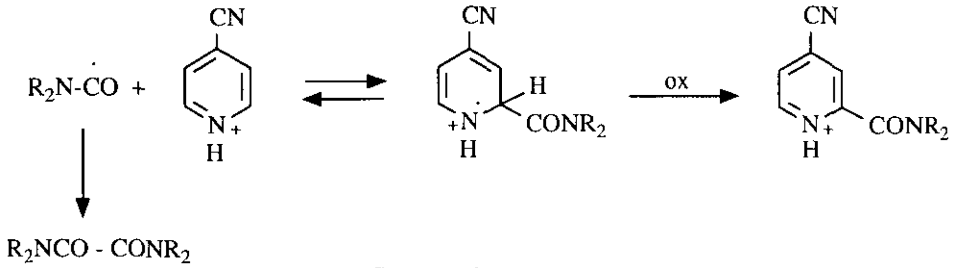
The mechanism of the reaction is similar to the general substitution mechanism of protonated heteroaromatic bases by nucleophilic radicals.[2] Compared to the mechanisms of eqs.(1) and (2), there is a difference concerning the source of carbamoyl radicals (eqs. 7 and 8).

$$S_2O_8^{=} + 2\ Ag\,(I) \longrightarrow 2\ SO_4^{=} + 2\ Ag\,(II) \qquad (7)$$

$$R_2NCOCOOH + Ag\,(II) \longrightarrow R_2N\dot{C}O + CO_2 + H^+ + Ag\,(I) \qquad (8)$$

Homolytic carbamoylation is much more effective and selective than alkoxycarbonylation by the corresponding radicals, obtained from a similar source[3] ($ROCOCOOH \longrightarrow RO\dot{C}O$); polar and enthalpic effects contribute to this behavior. The nucleophilic character of the carbonyl radicals (σ-radicals) increases in the series[4] $RO\text{-}\dot{C}O < R_2N\text{-}\dot{C}O < R\text{-}\dot{C}O$, whereas it increases according to the sequence $R_3\dot{C} < R_2\dot{C}\text{-}OR < R_2\dot{C}\text{-}NR_2$ with the alkyl radicals (π-radicals); this determines a higher selectivity by carbamoyl than by alkoxycarbonyl radicals. The decarboxylation of the alkoxycarbonyl radicals ($RO\dot{C}O \longrightarrow R\cdot + CO_2$), governed by enthalpic effects, limits the usefulness of alkoxycarbonylation.[3,5] The rates of decarboxylation (an irreversible process) are of the same order of magnitude than the rates of addition to the heterocyclic ring[3,5] (a reversible process[2]) when R is a benzylic, allylic, secondary or tertiary alkyl group. These limitations are negligible with carbamoyl radicals because the loss of CO ($R_2N\dot{C}O \longrightarrow R_2N\cdot + CO$) or R-N=C=O ($R_2N\dot{C}O \longrightarrow R\cdot + RN{=}C{=}O$) is not competitive for enthalpic reasons.

When two bulky alkyl groups are present in carbamoyl radicals, steric effects can influence the reversibility of the addition to the heterocyclic ring; this allows for a stationary concentration of the carbamoyl radical suitable for a competitive, irreversible dimerization (Scheme 1); this latter never occurs with monosubstituted alkyl or aryl carbamoyl radicals.



Scheme 1

The ratio between dimerization and heterocyclic substitution depends on the bulk of the alkyl group and on the reactivity of the heterocyclic ring; a higher reactivity (quinoxaline > quinoline > lepidine)[2] reduces reversibility and dimerization of the carbamoyl radical (Table 2).

Table 1 - Homolytic Carbamoylation of Heteroaromatic Bases

Heteroaromatic base	Carbamoyl radical	Conversion (%)	Orientation (%)	Yield[a] (%)
Lepidine	*N*-cyclohexyl	100	2	87
"	*N*-(*p*-chlorophenyl)	100	2	92
"	Piperidine	83	2	88
"	*N*,*N*-diisopropyl	18	2	90
"	*N*,*N*-dimethyl	51	2	94
Quinoline	*N*-cyclohexyl	100	2(80),4(20)	96
"	*N*-(*p*-chlorophenyl)	100	2	89
"	*N*,*N*-diisopropyl	66	2(88),4(12)	92
"	Piperidine	97	2	94
"	*N*,*N*-di-n-butyl	71	2	95
Quinoxaline	*N*-cyclohexyl	100	2	93
"	*N*-(*p*-chlorophenyl)	83	2	88
"	Piperidine	100	2(76);2,3(21)	96
"	*N*,*N*-diisopropyl	97	2	74
"	*N*,*N*-dimethyl	96	2	92
"	*N*,*N*-di-n-butyl	100	2	93
4-Cyanopyridine	*N*-cyclohexyl	100	2	95
"	*N*-(*P*-chlorophenyl)	97	2	91
"	*N*,*N*-diisopropyl	69	2	97
"	*N*,*N*-dimethyl	62	2	94
"	*N*,*N*-di-n-butyl	55	2	91
"	Piperidine	66	2	85
Benzothiazole	*N*-cyclohexyl	78	2	90
"	Piperidine	85	2	87
"	*N*,*N*-diisopropyl	45	2	94

a)Yields based on the conversion of the heteroaromatic bases.

Table 2 - Dimerization of Carbamoyl Radicals Versus Heteroaromatic Substitution (Scheme 1).

Heteroaromatic base	Carbamoyl radical	$(CONR_2)_2$ %	Het-$CONR_2$ %
Lepidine	Diisopropyl	78	22
Quinoline	"	40	60
Quinoxaline	"	1	99
4-Cyanopyridine	"	36	64
Lepidine	Piperidine	7	93
Quinoline	"	< 1	>99
Quinoxaline	"	-	100
4-Cyanopyridine	"	traces	~100
Lepidine	Dimethyl	10	90
Quinoxaline	"	-	100
Quinoline	Di-n-butyl	8	92
Quinoxaline	"	1	99
Lepidine	Cyclohexyl	-	100
Quinoxaline	"	-	100
Lepidine	*p*-Chlorophenyl	-	100
Quinoxaline	"	-	100

With quinoline, a high selectivity in position 2 and only minor amounts or traces of substitution in position 4 were observed. The factors affecting the α-γ ratio in the substitutions of the pyridine ring by alkyl and acyl radicals have been discussed previously.[2,6]

EXPERIMENTAL

General Procedure.

Cyclohexyl-, 4-chlorophenyl-, dimethyl-, di-n-butyl- and diisopropylamines, piperidine, oxalic acid monochloride monomethyl ester and oxalyl dichloride were Fluka commercial products. Oxalic acid monoamides were prepared by slight modifications of the known procedure:[7] 50 mmol of ClCO-COOMe and

65 mmol of pyridine were dissolved in 70 ml of CH_2Cl_2 at 0°C; then 55 mmol of the amine were dropped at 0°C; after 1h the mixture was allowed to reach room temperature; the precipitated pyridine hydrochloride was filtered and the CH_2Cl_2 solution was washed twice with 5% aqueous H_2SO_4, then with water till pH 7. The solvent was removed under vacuum and the residue was a substantially pure product (> 98 % purity by GC). This product was redissolved in 60 ml MeOH and a solution of 55 mmol of KOH in 50 ml MeOH was added by dropping at 15°C. After 30 minutes the precipitated R_2N-CO-COOK was filtered and washed with MeOH, hexane and Et_2O. It can be used as such for the reaction or hydrolyzed to obtain the free acid, using the following procedure: the potassium salt is dissolved in 50 ml of water, and the monoamide of oxalic acid is precipitated by addition of 10 % H_2SO_4 (30 mmol). The product, obtained in yields that in all cases are > 80 %, can be utilized for the reaction without further purification. The diamides of oxalic acid were prepared from the corresponding amines and oxalyl chloride according to the known procedure.[8]

Gc analyses were performed on a Dani 8610 gas chromatograph equipped with an OV 101 capillary column, a PTV injector and a flame ionization detector. Nmr spectra were recorded on a Bruker AC 250 MHz spectrometer; ms spectra were obtained on a Hitachi RMU-60 instrument.

Carbamoylation of heteroaromatic bases

1 mmol of heteroaromatic base, , 2 mmol of oxalic acid monoamide monopotassium salt (or of monoamide of oxalic acid), 3 mmol of $Na_2S_2O_8$ and 0.2 mmol of $AgNO_3$ were added to 7 ml of water containing 2 mmol of H_2SO_4 (or 1 mmol of H_2SO_4 in the case of monoamides of oxalic acid) and 7 ml of CH_2Cl_2. The mixture was refluxed for 1 h. The aqueous phase was made basic by 5% aqueous NaOH, the CH_2Cl_2 phase was separated and the aqueous phase was extracted twice with CH_2Cl_2. The evaporation of the solvent under vacuum provided the crude carbamoyl derivatives, which were purified by column chromatography on Merck kieselgel 60 (230-400 Mesh, ASTM), with a mixture of AcOEt/hexane 60:40 as eluent. Gc analysis was performed under the above mentioned conditions, utilizing *N,N*-dimethylbenzamide as internal standard. The carbamoyl derivatives of heteroaromatic bases were identified by Nmr and ms; the diamides of oxalic acid were identified by comparison with authentic samples. The results are reported in Tables 1 and 2.

Carbamoyl derivatives of 4-methylquinoline

N-Cyclohexyl: **^{1}H-Nmr** ($CDCl_3$) δ 8.20 (s broad, 1 H), 8.15 (d, 1 H, J = 0.4 Hz), 8.14-8.08 (dd, 1 H, J = 8.6 Hz, J = 1.2 Hz), 8.06-8.01 (dd, 1 H , J = 8.6 Hz, J = 1.2 Hz), 7.78-7.71 (m, 1 H), 7.66-7.58 (m, 1 H), 4.10-3.94

(m, 1 H), 2.76 (s, 3 H), 2.12-2.00 (m, 2 H), 1.88-1.74 (m, 2 H), 1.72-1.20 (m, 6 H); **^{13}C-nmr** ($CDCl_3$) δ 160.82 (C=O), 149.68 (CH, aromatic), 146,35 (C, aromatic), 145.94 (C, aromatic), 130.25 (CH, aromatic), 129.59 (CH, aromatic), 129.16 (C, aromatic), 127,40 (C, aromatic), 123.66 (CH, aromatic), 119.14 (CH, aromatic), 48.34 (CH-NH), 33.14 (2 CH_2), 25.64 (2 CH_2), 24.98 (CH_2), 18.88 (CH_3); **ms** m/z (rel. int.): 268 (M^+, 70), 240 (33), 215 (50), 143 (100). Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.08; H, 7.51; N, 10.44. Found: C, 76.18; H, 7.41; N, 10.47.

N-(4-Chlorophenyl): **Ms** m/z (rel. int.): 296 (M^+, 50), 253 (3), 169 (4), 143 (100), 115 (42). Anal. Calcd for $C_{17}H_{13}ClN_2O$: C, 68.80; H, 4.41; N, 9.44. Found : C, 68.68; H, 4,47; N, 9.46.

N,N-Diisopropyl: **Ms** m/z (rel. int.): 270 (M^+, 15), 255 (10), 227 (34), 213 (12), 185 (25), 170 (64), 143 (34), 115 (20), 100 (100). Anal. Calcd for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.62; H, 8.22; N, 10.22:

Piperidine: **Ms** m/z (rel. int.): 254 (M^+, 23), 183 (11), 170 (22), 143 (100), 115 (44). Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.02. Found: C, 75.48; H, 7.18; N, 11.12.

N,N-Dimethyl: **Ms** m/z (rel. int.): 214 (M^+, 16), 157 (16), 143 (100), 115 (35). Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.62; H, 6.63; N, 13.14.

Carbamoyl derivatives of quinoline

N-(4-Chlorophenyl): **^{1}H-Nmr** ($CDCl_3$) δ 10.24 (s broad, 1 H), 8.19-8.14 (d broad, 1 H, J = 8.5 Hz), 7.93-7.88 (dd, 1 H, J = 8.5 Hz, J = 1.2 Hz), 7.87-7.31 (m, 8 H); **ms** m/z (rel. int.): 283 (M^+, 40), 248 (7), 157 (11), 129 (100), 102 (12). Anal. Calcd for $C_{16}H_{11}N_2OCl$: C, 67.97; H, 3.92; N, 9.91. Found: C, 68.01; H, 4.00; N, 9.83.

Piperidine: **^{1}H-Nmr** ($CDCl_3$) δ 8.25 (d, 1 H, J = 8.5 Hz), 8.11 (dd, 1 H, J = 8.5 Hz, J = 1.0 Hz), 7.85 (dd, 1 H, J = 8.0, J = 1.0), 7.79-7.72 (m, 1 H), 7.66-7.56 (m, 2 H), 3.85-3.60 (m, 2 H), 3.55 (t, 2 H, J = 5.0 Hz), 1.8-1.6 (m, 6 H); **Ms** m/z (rel. int.): 240 (M^+, 9), 156 (5), 128 (100), 101 (26), 84 (58). Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 75.07; H, 6.65; N, 11.61.

N-Cyclohexyl: **Ms** m/z (rel. int.): 254 (M^+, 34), 226 (6), 211 (11), 197 (20), 173 (6), 156 (22), 143 (9), 128 (100), 101 (16), 98 (56). Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.02. Found: C, 75.46; H, 7.19; N, 11.06.

N,N-Diisopropyl: **Ms** m/z (rel. int.): 257 (M^+, 4), 242 (10), 214 (37), 200 (16), 186 (9), 157 (7), 129 (54), 101 (100). Anal. Calcd for $C_{16}H_{20}N_2O$: C, 74.96; H, 7.86; N, 10.93. Found: C, 75.18; H, 7.97; N, 10.76.

N,N-Di-n-butyl: **Ms** m/z (rel. int.): 285 (M^+,15), 242 (7), 186 (4), 157 (6), 129 (100), 103 (5), 102 (14). Anal.

Calcd for $C_{18}H_{24}N_2O$: C, 76.01; H, 8.50; N, 9.85. Found: C, 75.89; H, 8.53; N, 9.97.

Carbamoyl derivatives of quinoxaline

N,N-Diisopropyl: **^{1}H-Nmr** ($CDCl_3$) δ 9.02 (s, 1 H), 8.17-8.04 (m, 2 H), 7.87-7.74 (m, 2 H), 3.98-3.82 (m, 1 H), 3.66-3.48 (m, 1 H), 1.61 (d, 6 H, J = 6.0 Hz), 1.26 (d, 6 H, J = 6.0); **ms** m/z (rel. int.): 257 (M^+, 50), 242 (14), 214 (5), 157 (9), 129 (40), 100 (100). Anal. Calcd for $C_{15}H_{19}N_3O$: C, 70.01; H, 7.45; N, 16.33. Found: C, 70.18; H, 7.40; N, 16.25.

N-(4-Chlorophenyl): **^{1}H-Nmr** ($CDCl_3$) δ 9.88 (s broad, 1 H), 9.76 (s, 1 H), 8.26-8.16 (m, 2 H), 7.96-7.86 (m, 2 H); 7.83-7.77 (m, 2 H), 7.43-7.37 (m, 2 H); **ms** m/z (rel. int.): 283 (M^+, 34), 248 (7), 157 (10), 129 (100), 102 (21), 75 (12). Anal. Calcd for $C_{15}H_{10}ClN_3O$: C, 63.50; H, 3.55; N, 15.03. Found: C, 63.62; H, 3.52; N, 14.99.

Piperidine: **Ms** m/z (rel. int.): 241 (M^+, 56), 185 (4), 157 (9), 143 (4), 129 (90), 103 (100). Anal. Calcd for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.42. Found: C, 69.52; H, 6.32; N, 17.49.

N-Cyclohexyl: **Ms** m/z (rel. int.): 255 (M^+, 26), 157 (22), 129 (100), 103 (5). Anal. Calcd for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.50; H, 6.82; N, 16,42.

N,N-Dimethyl: **Ms** m/z (rel. int.): 202 (M^+, 60), 159 (10), 145 (22), 131 (100), 129 (32). Anal. Calcd for $C_{11}H_{11}N_3O$: C, 65.65; H, 5.50; N, 20.89. Found: C, 65.73; H, 5.46; N, 21.00.

N,N-Di-n-butyl: **Ms** m/z (rel. int.): 286 (M^+, 6), 243 (10), 158 (12), 131 (8), 129 (100), 103 (5), 102 (14). Anal. Calcd for $C_{17}H_{23}N_3O$: C, 81.23; H, 8.12; N, 14.73. Found: C, 81.12; H, 8.09; N, 14.78.

Carbamoyl derivatives of 4-cyanopyridine

N-(4-Chlorophenyl): **^{1}H-Nmr** ($CDCl_3$) δ 9.84 (s broad, 1 H), 8.83-8.80 (d, 1 H, J = 5.0 Hz), 8.53-8.51 (t, 1 H, J = 1.0 Hz), 7.73-7.60 (d, 1 H, J = 5.0 Hz), 7.75-7.69 (m, 2 H), 7.40-7.34 (m, 2 H); **ms** m/z (rel. int.): 257 (M^+, 10), 153 (100), 131 (50),103 (60). Anal. Calcd for $C_{13}H_8ClN_3O$: C, 60.59; H, 3.13; N, 16.31. Found: C, 60.48; H, 3.11; N, 16.51.

Piperidine: **Ms** m/z (rel. int.): 215 (M^+, 20), 159 (7), 131 (14), 104 (100), 103 (78). Anal. Calcd for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09; N, 19.53. Found: C, 67.11; H, 6.02; N, 19.41.

N-Cyclohexyl: **Ms** m/z (rel. int.): 229 (M^+, 70), 185 (50), 147 (99), 130 (85), 103 (100), 97 (99). Anal. Calcd for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.60; N, 18.33. Found: C, 67.97; H, 6.70; N, 18.42.

N,N-Diisopropyl: **Ms** m/z (rel. int.): 231 (M^+, 3), 216 (8), 188 (22), 174 (59), 146 (8), 131 (49), 104 (24), 103

(100), 100 (86). Anal. Calcd for $C_{13}H_{17}N_3O$: C, 67.50; H, 7.41; N, 18.17. Found: C, 67.33; H, 7.49; N, 18.21.

N,N-Dimethyl: **Ms** m/z (rel. int.): 176 (M^+, 33), 132 (6), 118 (5), 106 (4), 104 (100), 103 (52). Anal. Calcd for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99: Found: C, 61.59; H, 5.11; N, 24.15.

N,N-Di-n-butyl: **Ms** m/z (rel. int.): 259 (M^+, 3), 216 (8), 174 (5), 131 (21), 128 (100), 104 (10), 103 (35). Anal. Calcd for $C_{15}H_{21}N_3O$: C, 69.46; H, 8.16; N, 16.20. Found: C, 69.49; H, 8.06; N, 16.31.

Carbamoyl derivatives of benzothiazole

N-Cyclohexyl: **^{1}H-Nmr** ($CDCl_3$) δ 8.09-8.04 (dd, 1 H, J = 8.0 Hz, J = 1.2 Hz), 7.99-7.94 (dd, 1 H, J = 7.5 Hz, J = 1.7 Hz), 7.59-7.44 (m, 2 H), 7.34 (s broad, 1H), 4.08-3.90 (m, 1 H), 2.12-1.98 (m, 2 H), 1.86-1.72 (m, 2 H), 1.70-1.20 (m, 6 H); **Ms** m/z (rel. int.): 260 (M^+, 40), 232 (5), 215 (18), 203 (44), 178 (12), 162 (100), 149 (21), 135 (49), 134 (71). Anal. Calcd for $C_{14}H_{16}N_2OS$: C, 64.59; H, 6.19; N, 10.76. Found: C, 64.43; H, 6.06; N, 10.97.

Piperidine: **Ms** m/z (rel. int.): 246 (M^+, 37), 162 (59), 134 (100), 108 (12). Anal. Calcd for $C_{13}H_{14}N_2OS$: C, 63.39; H, 5.73; N, 11.38. Found: C, 63.21; H, 5.81; N, 11.52.

N,N-Diisopropyl: **Ms** m/z (rel. int.) 262 (M^+, 4), 219 (19), 205 (5), 177 (15), 162 (100), 136 (6),134 (38), 108 (7), 100 (40). Anal. Calcd for $C_{14}H_{18}N_2OS$: C, 64.09; H, 6.91; N, 10.68. Found: C, 63.98; H, 6.97; N, 10,82.

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