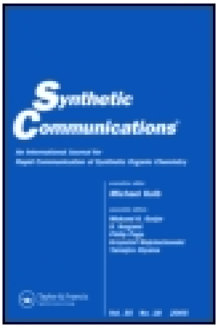

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An Efficient, One-Pot Synthesis of 3-Alkyl or Aryl Sydnoneimines

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AN EFFICIENT, ONE-POT SYNTHESIS OF 3-ALKYL OR ARYL SYDNONEIMINES

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Abstract: In a "one-pot" process, a variety of 3-alkyl and 3-aryl sydnoneimine hydrochlorides can be prepared in high yield, under mild conditions, by nitrosation of the corresponding aminoacetonitrile with isoamyl nitrite in diethyl ether followed by cyclization with HCl gas.

Sydnoneimine hydrochlorides **3**, members of the class of unique, dipolar heterocycles known as mesoionic compounds[1], have been extensively studied[2] since their first preparation in 1957.[3] A considerable part of the interest in such species stems from their potent biological properties. Thus, many sydnoneimine salts and their exocyclic derivatives exhibit hypotensive activity, the most pronounced effects being apparent in 3-amino substituted derivatives.[4] One substance, N-6-ethoxycarbonyl-3-morpholinosydnoneimine, molsydomine,[5] has been employed as a hypotensive drug. Monoamine oxidase inhibition by a number of sydnoneimines has been reported[6] and, in this regard, 3-phenylisopropyl-sydnoneimine (sydnophen) and N(6)-phenylcarbamoyl-3-phenylisopropyl-sydnoneimine (sydnocarb) have found application as psychostimulators in the treatment of various mental illnesses.[7]

The only general route to sydnoneimine hydrochlorides **3** involves treatment of an N-substituted aminoacetonitrile **1** with nitrous acid to form the corresponding

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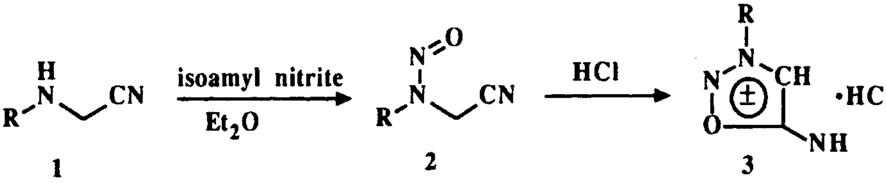
N-nitroso compound **2**, followed by cyclization with hydrogen chloride in various solvents.[3a,8] While "one-pot" nitrosation / cyclization has been mentioned briefly for cases where isolation of the intermediate N-nitroso species **2** is difficult[2], no general protocol has been developed nor has a convenient organic soluble reagent such as isoamyl nitrite been employed. The advantages to such a process would accrue from the excising of an isolation step (of **2**) [and the resultant, safer handling of the potentially carcinogenic N-nitrosamines **2**].

Recently, we reported[9] that sydnones [O(6) congeners of sydnoneimines] could be prepared efficiently, under mild, neutral conditions using isoamyl nitrite in dimethoxyethane. We have now shown that sydnoneimines **3** can be synthesized similarly using the same reagent in ether (followed by HCl cyclization) in a "one-pot", high yield process from N-substituted aminoacetonitriles **1**.



1-3	R	1-3	R
a	i-Pr	e	Ph
b	n-Bu	f	4-$CH_3C_6H_4$
c	s-Bu	g	4-$CH_3OC_6H_4$
d	$PhCH_2$	h	3-ClC_6H_4

Overall, the process is effective for the preparation of variously substituted sydnoneimines under mild conditions. The yields are excellent (even the lowest yield process; *viz.* for **3c** - 71%, is equivalent to an 84% yield for each individual step) and, unlike the "normal" nitrosation / cyclization process, the toxic N-nitroso species **2** do not have to be isolated and, on account of the neutral conditions for the nitrosation, the progress of the nitrosation step can be monitored by thin layer chromatography.

Table. Preparation of Sydnoneimine Hydrochlorides 3

Product	Overall[a] Yield (%)	Reaction Time for nitrosation (h)	m.p. (°C)	Lit. m.p. (°C)
3a	73	2	140-1	141-2[10]
3b	79	2	145-6	145-6[11]
3c	71	3	113-4	116-7[6]
3d	90	12	118-9	111-2[12]
3e	93	2	180-1	180-1[11]
3f	77	2	190-1	191-3[11]
3g	80	2	192-3	192-4[11]
3h	72	3	172-4	167-8[13]

[a] The yields given are for the 2 step conversion of the aminoacetonitrile **1** to the sydnoneimine **3** and represent the average of 3 runs

EXPERIMENTAL

Conversion of N-Substituted Aminoacetonitriles to 3-Substituted Sydnoneimines; General Procedure.

To a stirred solution of the aminoacetonitrile **1** (0.005mol) in diethyl ether (2-5mL) was added isoamyl nitrite (0.0075mol). After the reaction was complete (2-12h, TLC, solvent: petroleum ether : ether, 2:1), hydrogen chloride was bubbled gently through the mixture until the N-nitroso intermediate **2** had completely reacted (usually 5-10min., TLC). On cooling in ice, the crude sydnoneimine crystallized out, was collected by filtration, washed with petroleum ether / ether (1:1) and recrystallized from isopropanol or absolute ethanol.

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