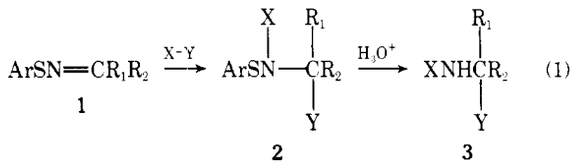
Synthesis of Secondary and Tertiary Carbinamines from N-Alkylidenearenesulfenamides and Alkyl- and Aryllithium Reagents

Summary: A one-step synthesis of secondary and tertiary carbinamines from *N*-alkylidenearenesulfenamides **1** and alkyl and aryllithium reagents is described which illustrates the synthetic value of **1** as "masked" imine derivatives of ammonia.

Sir: The importance of the imine (azomethine) group in organic synthesis is well documented.[1] Its use, however, is generally restricted to N-substituted imines since imines of ammonia (>C=NH) are easily hydrolyzed and undergo self-condensation reactions.[1a,b] *N*-Alkylidenearenesulfenamides[2] **1** may potentially act as "masked" imine derivatives of ammonia. Addition of a reagent X–Y to the C–N double bond in **1** would yield a sulfenamide **2**,[3] and the relatively weak S–N

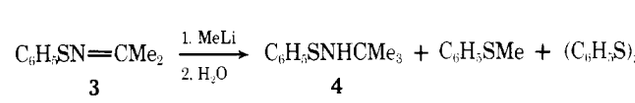


(1)

bond in **2** may be cleaved to yield the free amine derivative (eq 1). *N*-Alkylidenearenesulfenamides **1** are considerably more resistent to hydrolysis than imines, can be stored indefinitely at 10–20 °C, and are conveniently prepared in good yield from disulfides, aldehydes or ketones, silver nitrate, and ammonia.[2]

Current methods for preparing primary amines include the Gabriel synthesis and the Leuckart, Hofmann, Curtius, and Schmidt reactions.[4] Many of these procedures are inconvenient, often hazardous, and limited to specific classes of compounds. The reductive amination of ketones with sodium cyanoborohydride gives good yields of secondary carbinamines, but fails with hindered and diaryl ketones.[5] The Ritter reaction is the only convenient method for preparing tertiary carbinamines, but generally requires the presences of strong acids.[6]

We wish to report a convenient "one-step" synthesis of secondary and tertiary carbinamines from **1** and alkyl- and aryllithium reagents using the reaction sequence described in eq 1. Reaction of methyllithium with *N*-isopropylidenebenzenesulfenamide **3**[2] gave, after hydrolysis, sulfenamide **4**[7]



(78%), thioanisole (~1%), and diphenyl disulfide (~2%). Maximum yields of **4** were obtained when 2 equiv of methyllithium were added to **3** and the mixture was allowed to stand for 1.5 hr at room temperature and then refluxed for 0.5 hr. Lower temperatures and the addition of TMEDA reduced the yield of **4**.[8]

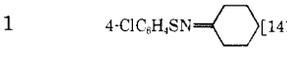
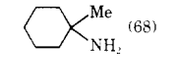
The amine may be isolated in "one step" from **1** and the alkyl- or aryllithium reagent; the procedure is illustrated for the synthesis of 2-phenyl-2-aminopropane (Table I, entry 7).

In a 500-ml, 3-necked flask equipped with magnetic stir bar and nitrogen and syringe inlets were placed 10 mmol of isopropylidenebenzenesulfenamide (**3**) in 100 ml of dry ether. Phenyllithium (20 mmol) was added via syringe with cooling. After stirring for 1 hr at room temperature and for 0.5 hr at reflux, the reaction mixture was cautiously hydrolyzed with 100 ml of water. The two-phase mixture was separated and the organic phase washed with 6 N HCl (3 × 10 ml). The acid solution was removed under vacuum to yield the crude, solid amine hydrochloride. The amine hydrochloride was treated with 20 ml of 20% sodium hydroxide solution and the free amine extracted into ether (3 × 20 ml). After drying over $MgSO_4$ removal of solvent gave 0.8 g (61%) of an oil, bp 70–73 °C (8 mm) [lit.[9] 72–73 °C (8 mm)], identified as 2-phenyl-2-aminopropane. The amine obtained by this procedure prior to distillation was 96% pure as indicated by NMR and GLC.

Using this procedure the synthesis of secondary and tertiary carbinamines from **1** and alkyl- and aryllithium reagents is summarized in Table I. Amines obtained by this method were essentially pure (>97%), as indicated by NMR, GLC, and TLC, and were identified by comparison of their properties with literature values. As Table I indicates, this method for amine synthesis gave good yields of amines even with *tert*-butyllithium (entries 4 and 8). In general, yields of amines using this "one-step" procedure were better and in many cases more convenient than the multistep methods reported in the literature (Table I).

The one-step preparation of amines from **1** and alkyl- and aryllithium reagents represents a new and convenient synthesis of hindered secondary and tertiary carbinamines from a novel substrate. Overall, the reaction (eq 1) results in the conversion of a carbonyl group to a secondary or tertiary carbinamine and demonstrates the potential synthetic utility

Table I. Synthesis of Amines from *N*-Alkylidenearenesulfenamides **1**

Entry	Sulfenamide[a] [bp, °C (mm), % yield]	Lithium reagent[b]	Amine (% yield)[c]	Ref
1	$C_6H_5SN{=}CHC_6H_5$ [70%][d]	MeLi	$C_6H_5C(Me)HNH_2$ (79)	*e*
2		*n*-BuLi	$C_6H_5C(CH_2CH_2CH_2CH_3)HNH_2$ (70)	*f*
3		C_6H_5Li	$(C_6H_5)_2CHNH_2$ (59)	*g*
4		Me_3CLi	$C_6H_5C(CMe_3)HNH_2$ (87)	*h*
5	$C_6H_5SN{=}CHMe$ [64–65 (0.04), 52]	C_6H_5Li	$C_6H_5C(Me)HNH_2$ (61)	*e*
6	$C_6H_5SN{=}CMe_2$	*n*-BuLi	$CH_3CH_2CH_2CH_2C(NH_2)(Me)_2$ (57)	*i*
7		C_6H_5Li	$C_6H_5C(NH_2)(Me)_2$ (61)	*j*
8		Me_3CLi	$Me_3CC(NH_2)(Me)_2$ (43)	*k*
9	$C_6H_5SN{=}C(Me)CH_2CH_3$ [73 (0.1), 97]	C_6H_5Li	$C_6H_5C(Me)(CH_2CH_3)NH_2$ (83)	*l*
10	$4\text{-}ClC_6H_4SN{=}CMeC_6H_5$ [58–60, 62]	MeLi	$C_6H_5C(NH_2)Me_2$ (59)	*j*
11	 [141 (0.15), 45]	MeLi	 (68)	*m*

[a] Reference 2 unless otherwise noted. [b] Aldrich Chemical Co. [c] Isolated yields; reactions run at least twice and yields averaged. [d] See also F. A. Davis, J. M. Kaminski, E. W. Kluger, and H. S. Freilich, *J. Am. Chem. Soc.*, **97**, 7085 (1975). [e] Reference 5. [f] A. de Roocker and P. de Radzitsky, *Bull. Soc. Chim. Belg.*, **82**, 195 (1963); *Chem. Abstr.*, **59**, 9845h (1963). [g] J. Kalaman and B. Ryban, *Chem. Zvesti*, **20**, 79 (1966); *Chem. Abstr.*, **64**, 17453e (1966). [h] H. Christol, A. Lavrent, and M. Mousseron, *Bull. Chem. Soc. Fr.*, 2319 (1961); *Chem. Abstr.*, **56**, 14133 (1962). [i] *Zh. Obshch. Khim.*, **29**, 174 (1959); *Chem. Abstr.*, **53**, 21661h (1959). [j] Reference 6. [k] J. W. Timberlake, M. L. Hodges, and K. Betterton, *Synthesis*, 633 (1972). [l] D. J. Cram, C. A. Kingsburg, and A. Langemann, *ibid.*, **81**, 5785 (1959). [m] P. Kovacic and S. S. Chaudhary, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 35.

of *N*-alkylidenearenesulfenamides as "masked" imine derivatives of ammonia.

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References and Notes

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(7) F. A. Davis, A. J. Friedman, E. W. Kluger, E. B. Skibo, E. R. Fretz, A. P. Milicia, W. C. LeMasters, M. D. Bentley, J. A. Lacadie, and I. B. Douglas, *J. Org. Chem.*, in press.
(8) Products were analyzed by gas chromatography on a 6-ft 6% OV-17 on 60/80 mesh Chromosorb W (regular) column by comparison of peak areas with standard solutions of reaction products. Analysis were performed at least twice and the results averaged. With 2 equiv of MeLi at −78 °C for 4 h, **3** gave 48% **3** and 50% **4**. With 2 equiv each of MeLi and TMEDA at 25 °C, **3** gave 38% **3** and 58% **4**.
(9) A. C. Cope, T. T. Foster, and P. H. Towle, *J. Am. Chem. Soc.*, **71**, 3929 (1949).

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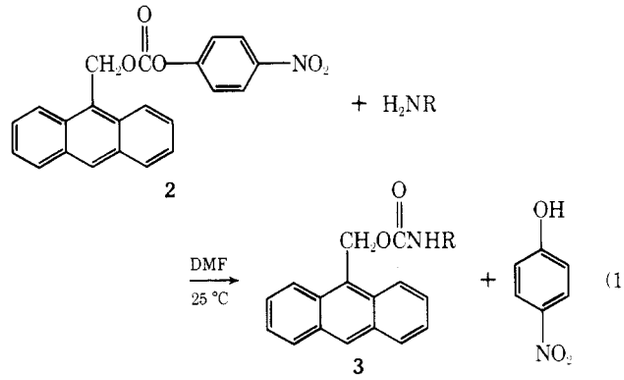
A New Method for Protecting Amines

Summary: A new method for protecting amines which hinges on the unusual chemical properties of the 9-anthrylmethyl system is described.

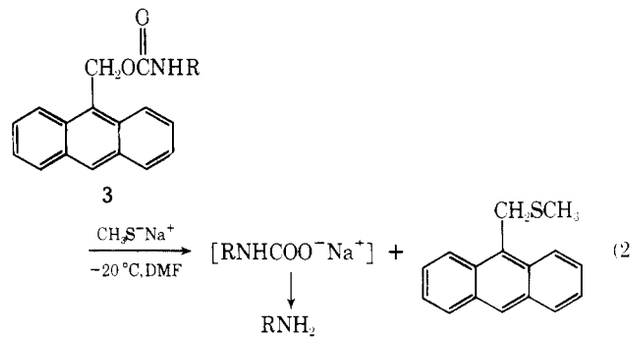
Sir: The 9-anthrylmethyl system **1** provides an excellent blocking group for carboxylic acids, phenols and thiophenols.[1] We now describe a simple procedure for protecting amines[2] which is based on their conversion to 9-anthrylmethyl carbamates **3**. Such carbamates are readily produced at room temperature by treating the amine with 9-anthrylmethyl *p*-nitrophenyl carbonate **2** (eq 1).[3]

1



(1)

Deblocking does not rely on the carbamate function but, rather, on a special property of the 9-anthrylmethyl system. What is invoked is a new type of substitution at a saturated carbon atom attached to the 9 position of the anthracene nucleus; these reactions are noteworthy for the speed with which they occur under mild conditions.[1,4] Removal of the protective group is achieved by treating the 9-anthrylmethyl carbamate with the sodium salt of methyl mercaptan (eq 2).

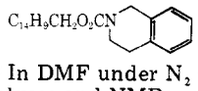


(2)

At −20 °C the reaction requires from 1 to 7 h; at 25 °C it is complete in <4 min. The results obtained with a wide variety of carbamates are summarized in Table I; the yields refer to pure, isolated amines.

Despite the ease with which these compounds are deblocked by the sodium salt of methyl mercaptan they are resistant to the action of various bases and acids. Thus, the 9-anthrylmethyl carbamates derived from *n*-octylamine, di-*n*-octylamine, and *p*-phenetidine are unaffected by exposure for 24 h to 30 mol of anhydrous ethylamine in DMF at 25 °C. They are also unaffected by 2 equiv of lithium hydroxide (0.01 N) in aqueous dioxane after 6 h at 25 °C. These carbamates are also stable to 4 equiv of sulfuric acid (0.10 N) in aqueous dioxane for 1 h at 25 °C, and they are not affected by 10 equiv of trifluoroacetic acid (1.0 M) in dioxane after 1 h at 25 °C.

Table I. The Deblocking of 9-Anthrylmethyl Carbamates By The Sodium Salt of Methyl Mercaptan[a,b]

9-Anthrylmethyl carbamate (3)	Amine	% yield	Reaction time, hr
$C_{14}H_9CH_2O_2CNH(CH_2)_7CH_3$	*n*-Octylamine	77	7
$C_{14}H_9CH_2O_2CNH(CH_2)_2C_6H_4Cl$	2-(*p*-Chlorophenyl)ethylamine	86	*c*
$C_{14}H_9CH_2O_2CNHCH_2C_6H_4Cl$	*p*-Chlorobenzylamine	82	1
$C_{14}H_9CH_2O_2CNHCH(C_6H_5)_2$	Benzhydrylamine	97	5
$C_{14}H_9CH_2O_2CNHC_6H_4OC_2H_5$	*p*-Phenetidine	91	3
$C_{14}H_9CH_2O_2CN[(CH_2)_7CH_3]_2$	Di-*n*-octylamine	85	*c*
	Tetrahydroisoquinoline	86	2

[a] In DMF under N_2 0.3 M in carbamate and 0.6 M in CH_3SNa; at −20 °C unless otherwise stated. [b] Satisfactory elemental analyses and NMR and IR spectra were obtained for all new compounds. [c] 4 min at 25 °C.