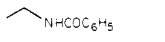
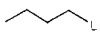
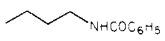
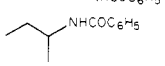
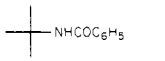
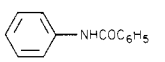
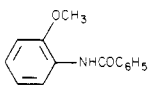
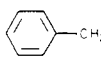
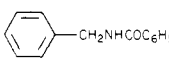
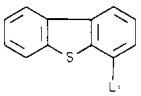
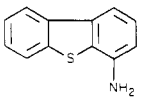
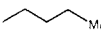
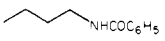
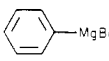
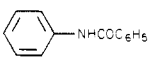
A Modification of the Sheverdina-Kocheshkov Amination: The Use of Methoxyamine-Methyllithium as a Convenient Synthetic Equivalent for NH_2^+

Summary: Direct stoichiometric amination of organolithiums can be achieved in high yields by methoxyamine and methyllithium in hexane–ether. The synthetic advantages of this approach are noted.

Sir: The interest in achieving direct amination of organometallics is indicated by the continuing development of a variety of methods for this conversion.[1-3] The use of methoxyamine, one of the first and most general reagents for this purpose,[1] has not been attractive because at least 2 equiv of the organometallic to be aminated appear to be required.[1b,4] We herein report that the use of methoxyamine–methyllithium provides an effective method for the direct stoichiometric conversion of an organolithium to the corresponding amine.

Treatment of 2 equiv of methoxyamine in hexane with 2 equiv of methyllithium in ether at −78 °C followed by addition of 1 equiv of an organolithium reagent, stirring at −15 °C for 2 h, and an aqueous quench gives the corresponding amines which were converted to the benzamides for isolation. High yields are obtained with primary, secondary, and tertiary alkyl and aryl organolithiums as shown in Table I. Grignard reagents react less effectively under the present conditions. The absence of methyllithium, the use of *n*-butyl- or phenyllithium in the first step, or a different solvent system results in reduced yields of products.[5] For amination of a specific organolithium the present reaction offers advantages in yield, convenience, and reagent availability over alternative methodology.[6,7]

Table I. Reactions of Organolithium and Grignard Reagents with Methoxyamine–Methyllithium

organometallic	amide	% yield[a,b]
CH_3Li	$CH_3NHCOC_6H_5$	80
		78
		77[c]
		67
		80
		90
		96
		97
		55[c,d]
		16[c]
		37[c]

[a] The yields are based on organometallic. [b] Benzamides were characterized by melting point and spectral criteria as pure compounds. [c] The temperature was held at −15 °C for 30 min followed by heating to reflux for 1 h. [d] Isolated as the amine.

$$RLi \xrightarrow[2.\ H_2O]{1.\ CH_3ONH_2\text{–}CH_3Li} RNH_2 \xrightarrow{C_6H_5COCl} RNHCOC_6H_5$$

R = alkyl, aryl

Although the focus of this report is on synthetic utility, the mechanism of the reaction is intriguing. Direct displacement on methoxyamine or its derivative or reaction via a nitrenoid species appear to be limiting possibilities. We are exploring extensions of this methodology to other nucleophiles and alkoxyamines and investigating the reaction mechanism.

Amination of Phenyllithium. A stirred 9.2-mL (0.0085 mol) sample of a 0.92 M solution of methyllithium in ether was cooled to a −78 °C, under a nitrogen atmosphere, and a solution of 0.4 g (0.0085 mol) of methoxyamine in 9 mL of hexane was added dropwise (1 drop/s) followed by 2.8 mL (0.0043 mol) of a 1.55 M solution of phenyllithium in 30:70 ether/cyclohexane. The mixture

(1) For formal displacements on methoxyamine, see (a) Sheverdina, N. J.; Kocheshkov, Z. *J. Gen. Chem. USSR* **1938**, *8*, 1825. (b) Brown, R.; Jones, W. E. *J. Chem. Soc.* **1946**, 781. (c) Willis, H. B. *Chem. Abstr.* **1944**, *38*, 739. (d) Gilman, H.; Ingham, R. *J. Am. Chem. Soc.* **1953**, *75*, 4843. (e) Gilman, H.; Avakian, S. *Ibid.* **1946**, *68*, 1514. (f) Gilman, H.; Avakian, S. *Ibid.* **1946**, *68*, 580. (g) Silver, M. *Ibid.* **1960**, *82*, 2646. (h) Silver, M. *Ibid.* **1961**, *83*, 3487. (i) Yamada, S.-I.; Oquri, T.; Shioiri, T. *J. Chem. Soc., Chem. Commun.* **1972**, *10*, 623. (j) Yamada, S.-I; Oquri, T.; Shioiri, T. *Chem. Pharm. Bull.* **1975**, *23*, 167. (k) Yamada, S.-I.; Oquri, T.; Shioiri, T. *Ibid.* **1975**, *23*, 173.

(2) For formal displacements on other sp^3 nitrogens, see the following, (a) Chloramine: Coleman, G. H.; Yager, R. *J. Am. Chem. Soc.* **1929**, *51*, 567. Coleman, G. H; Hermanson, J. L.; Johnson, H. L. *Ibid.* **1937**, *59*, 1896. (c) *N,N*-Dialkyl-*O*-(mesitylenesulfonyl)hydroxylamine: Boche, G. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 687. (b) *O*-(2,4-Dinitrophenyl)-hydroxylamine: Miller, M. J.; Loudon, G. M.; Radhakrishna, A. S. *J. Org. Chem.* **1979**, *44*, 4836. (c) Hydroxylamine-*O*-sulfonic acid: Wallace, R. G. *Aldrichimica Acta* **1980**, *13*, 3. Yamada, S.; Oquri, T.; Shiori, T. *J. Chem. Soc., Chem. Commun.* **1972**, 623. (d) *O*-(Meistylenesulfonyl)-hydroxylamine: Tamura, Y.; Minamikowa, J.; Ikeda, M. *Synthesis* **1977**, *1*, 1. Edwards, J. A.; Kluge, A. F.; Scopes, D. C. *J. Org. Chem.* **1977**, *42*, 376. (e) Primary and secondary amines with organocopper reagents and oxygen: Yamamoto, H.; Maruoka, K. *J. Org. Chem.* **1980**, *45*, 2739 and references cited therein.

(3) For formal additions to sp^2 nitrogen, see the following. (a) Acetone oxime: Alvernhe, G.; Laurent, A. *Tetrahedron Lett.* **1972**, 1007. (b) Phenyldiazonium salts: Garst, M. E.; Lukton, D. *Synth. Commun.* **1980**, *10*, 155. (c) Azidomethyl phenyl sulfide: Trost, B. M.; Pearson, W. H. *J. Am. Chem. Soc.* **1981**, *103*, 2483. (d) Hassner, A.; Murger, P.; Belinha, B. A. *Tetrahedron Lett.* **1982**, 699.

(4) In one case Sheverdina and Kocheskov report a 71% yield on amination of isoamylmagnesium bromide with 1 equiv of methoxyamine. Our attempts to use 1 equiv of methoxyamine provided lower yields than in Table I but this point is still under investigation.

(5) For example, in experiments similar to those in Table I we find the following: the use of *n*-butyllithium–methoxyamine followed by ethyllithium and benzoylation gives 76% *N*-*n*-butylbenzamide and 3% *N*-ethylbenzamide; the reaction of 2 equiv of methoxyamine with *n*-butyllithium followed by benzoylation provides 17% *N*-*n*-butylbenzamide; however, the use of 1 equiv of methoxyamine in the same sequence gives 64% *N*-*n*-butylbenzamide; the use of 1 equiv of methoxamine with phenyllithium provides 37% *N*-phenylbenzamide. These observations might be rationalized on the basis of different solubilities and competing mechanisms, but further work will be necessary to establish the reaction pathway of the amination.

(6) Commercially available methyllithium in ether, both salt free and containing lithium bromide, has been used with success. Methoxyamine was obtained by fractional distillation of a mixture of dimethylformamide–sodium hydroxide and the commercially available hydrochloride salt. Professor R. Quirk has found distillation from degassed polyethylene oxide–KOH on a vacuum line is effective. We are grateful to Professor Quirk for this information.

(7) The following yields for previous reports are calculated on the basis of the organolithium aminated. Phenyl-, *n*-butyl-, and methyllithium were converted to the corresponding amines with chloroamine in 3%, 7%, and 4% yields, respectively.[2a] Two equivalents of phenyllithium was converted to aniline with 1 equiv methoxyamine in 32% yield.[1a] Two equivalents of 4-lithiodibenzothiophene was converted to 4-aminodibenzothiophene with 1 equiv methoxyamine in 32% yield.[1b] From *o*-lithioanisole, which was converted to the Grignard reagent with anhydrous magnesium bromide, 2-aminoanisole was obtained, upon reaction with azidomethyl phenyl sulfide, in two steps, in an overall yield of 77%.[3c]

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was warmed to −15 °C for 2 h and quenched with 0.5 mL of water, and a solution of 7 mL of pyridine in 6 mL of ether was added, followed by a solution of 1.9 mL of benzoyl chloride in 7 mL of ether, and the solution was stirred overnight. Extractive workup with chloroform provided a yellow solid which was chromatographed on a medium-pressure silica gel column using 20% ethyl acetate in hexane as eluant to provide 0.76 g (90%) of analytically pure *N*-phenylbenzamide as a white solid, mp 161.5–163 °C (lit.[8] mp 163 °C).

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Registry No. Methoxyamine, 67-62-9; methyllithium, 917-54-4; ethyllithium, 811-49-4; butyllithium, 109-72-8; (1-methylpropyl)lithium, 598-30-1; (1,1-dimethylethyl)lithium, 594-19-4; phenyllithium, 591-51-5; (2-methoxyphenyl)lithium, 31600-86-9; (phenylmethyl)-lithium, 766-04-1; dibenzothiophene-4-yllithium, 75288-58-3; 1-bromobutane, 109-65-9; bromobenzene, 108-86-1; *N*-methylbenzamide, 613-93-4; *N*-ethylbenzamide, 614-17-5; *N*-butylbenzamide, 2782-40-3; *N*-(1-methylpropyl)benzamide, 879-71-0; *N*-(1,1-dimethylethyl)benzamide, 5894-65-5; *N*-phenylbenzamide, 93-98-1; *N*-(2-methoxyphenyl)benzamide, 5395-00-6; *N*-(phenylmethyl)benzamide, 1485-70-7; 4-dibenzothiophenamine, 72433-66-0.

(8) "Handbook of Chemistry of Physics", 45th ed.; Weast, R. C., Ed.; The Chemical Rubber Co.: Cleveland, OH, 1964; p C-181.

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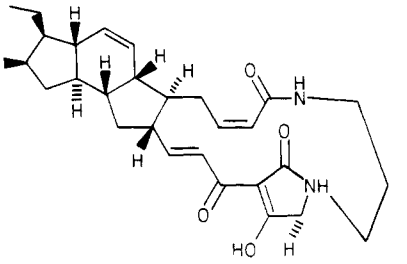
Methodology for the Synthesis of Phosphorus-Activated Tetramic Acids: Applications to the Synthesis of Unsaturated 3-Acyltetramic Acids[1]

Summary: A general method is described for the preparation of phosphonate-activated 3-acetyltetramic acids from a variety of α-amino esters, which can serve as precursors of enoyl and dienoyl tetramic acids which are found in a number of natural products.

Sir: As part of a research program directed toward the synthesis of tetramic acid containing natural products such as ikarugamycin (**1**)[2] and tirandamycin (**2**),[3] we required a general method for construction of unsaturated 3-acyltetramic acids which would fulfill several requirements. Among these requirements were the following: (1) the use of α-amino acids as starting materials in order to take advantage of this pool of optically active starting materials, (2) the use of mild conditions to prevent racemization, (3) the specific activation of the terminal acetyl methyl for



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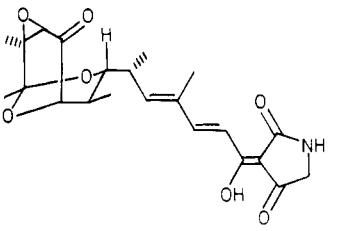

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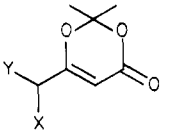
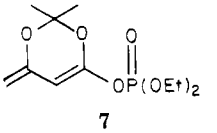
olefin formation prior to generation of the heterocyclic nucleus, (4) sufficiently high reactivity of the activated derivative permitting olefination under mild conditions. These restrictions were deduced in part from the studies of Rinehart who demonstrated that direct acylation of unsaturated acid fluorides and chlorides was not feasible nor was functionalization (halogenation) or condensation (with aldehydes) of the intact tetramic acids.[4,5] Furthermore, construction of the heterocycle after olefination was not feasible due to the severity of the conditions required for condensation of the unsaturated β-keto esters with amino esters.[5]

Given these considerations, we sought to prepare a protected β-keto ester already activated for olefin formation, which would have sufficient reactivity utilizing weak acid catalysis, to condense with a variety of α-amino esters to afford the corresponding β-keto amide. Two such substances which appeared to fulfill these requirements were the phosphonate **3** and phosphorane **4**.





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3, X = H; Y = P(=O)(OEt)$_2$
4, X = Y = PPh$_3$
5, X = Y = H
6, X = H; Y = Br
8, X = H; Y = Cl

We hoped to prepare these substances from the readily available unsubstituted system **5** obtained from diketene and acetone (91%).[6] Our initial attempt involved conversion to bromide **6** with NBS (CCl_4/$h\nu$/peroxide) in 83% yield. Bromide **6** underwent smooth conversion to phosphorane **4** upon treatment with triphenylphosphine in benzene followed by exposure to aqueous base (~90% overall). Phosphorane **4** reacts with aldehydes as expected, but the difficulties associated with isolation and manipulation of the ylide products led us to carry on our explorations in the phosphonate series.

(1) These studies were performed in part at Wayne State University, Department of Chemistry and form part of a dissertation submitted to Wayne State University by A.J.T. in partial fulfillment of the requirements for the Ph.D.

(2) (a) Ito, S.; Hirata, Y. *Bull. Soc. Chem. Jpn.* **1977**, *50*, 227. (b) *Ibid.* **1977**, *50*, 1813.

(3) (a) MacKellar, F. A.; Grostic, M.; Olson, E.; Wnuk, R.; Branfman, A.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1971**, *93*, 4943. (b) Duchamp, D. J.; Branfman, A. R.; Button, A. C.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 4077.

(4) (a) Van Der Baan, J. L.; Barnick, J. W.; Bickelhaupt, F. *Tetrahedron* **1978**, *34*, 223. (b) Yamaguchi, T.; Saito, K.; So, K.; Takeshita, M.; Tsujimoto, T.; Yuki, H. *J. Pharm. Soc. Jpn.* **1976**, *96*, 927.

(5) (a) Lee, V. J.; Braufman, A. R.; Herrin, T. R.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 4225. (b) Lee, V. T. PhD. Dissertation, University of Illinois, Urbana, IL, 1975.

(6) Carroll, M. F.; Bader, A. R. *J. Am. Chem. Soc.* **1953**, *75*, 5400.

0022-3263/82/1947-2823$01.25/0