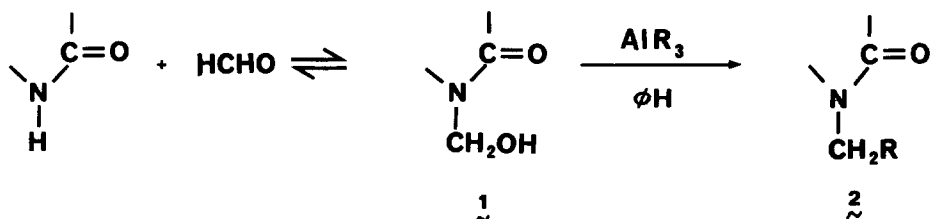


N-ALKYLATION OF AMIDES AND RELATED COMPOUNDS

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Relatively few reliable methods are currently available for the mono-N-alkylation of amides, lactams, ureas, carbamates and other similar types of functionality.²⁻⁴ We recently reported⁴ two methods for N-methylation of such compounds via reduction of

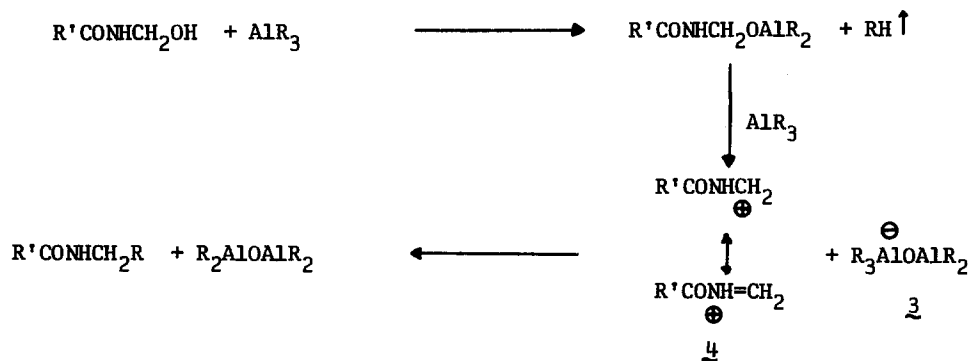


methylols (1), which are readily prepared by condensation of the parent amido compound with formaldehyde.⁵ In general, aldehydes other than formaldehyde cannot be used to prepare alkyl substituted analogs of methylol 1, and therefore our reduction procedures⁴ are not applicable for preparation of higher N-alkyl amide homologs.

We have found that simple amide methylols (1) can be directly coupled with trialkylaluminum reagents to produce higher N-alkyl compounds (2) in good yield. For example, treatment of benzamide methylol with trimethylaluminum in benzene produces N-ethylbenzamide. We have also tested this procedure with triethylaluminum and triisobutylaluminum, producing the N-propyl and N-isopentyl amides, respectively. The best yields have been obtained using four equivalents of alkylaluminum in refluxing benzene (vide infra). This two step alkylation sequence works equally well for ureas and carbamates. Table 1 shows the methylols which were studied and the isolated yields of N-alkylated products. Inexplicably, pyrrolidone methylol gives only poor yields of coupled products, although this was the only lactam methylol we attempted to alkylate.

We speculate that this coupling reaction proceeds through the mechanism outlined below. The key step involves the transfer of an alkyl group from an aluminumate complex 3

to an electrophile $\underline{4}$.^{6,7} Acyl iminium ions such as $\underline{4}$ are believed to be intermediates in the well known amidoalkylation reactions of methylols (Tscherniac-Einhorn Reaction).^{5,9}



In a typical experiment one mmole of methylol⁸ in 10 ml of dry benzene is cooled in ice and 4 mmol of trialkyl aluminum (25% in hexane from Alfa Inorganics) is added slowly with a syringe during which time gas evolution is observed. The reaction mixture is heated under reflux for 6-10 hours, cooled, and dilute HCl is added. The mixture is extracted with chloroform and the organic extract is dried and evaporated to afford nearly pure alkylated product in most cases. The crude product can be purified further by recrystallization or distillation if desired.


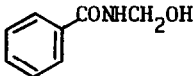
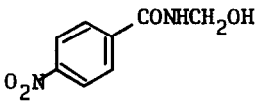
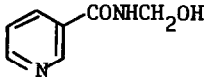
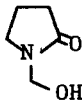
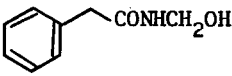
Acknowledgment

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References and Notes

- (1) Fellow of the A.P. Sloan Foundation, 1975-77; Recipient of an NIH Career Development Award (HL-00176), 1975-80.
- (2) I.T. Harrison and S. Harrison, "Compendium of Organic Synthetic Methods," Vol. 1, Wiley-Interscience, New York, N.Y., 1971, pp 211-212.
- (3) L. Bernardi, R. DeCastiglione, and U. Scarponi, *J. Chem.Soc., Chem.Comm.*, 320 (1975).
- (4) J. Auerbach, M. Zamore and S.M. Weinreb, *J.Org.Chem.*, **41**, 725 (1976).
- (5) (a) H.E. Zaugg and W.B. Martin, *Org. React.*, **14**, 52 (1965); (b) H. Hellmann and G. Opitz, "α-Aminoalkylierung", Verlag Chemie, Weinheim, Germany, 1960.

Table 1. Reaction of Methylols with Four Equivalents of Trialkyl Aluminum in Refluxing Benzene.⁸

<u>Methylol</u>	% Isolated Yield of N-Alkylated Product ^a		
	<u>(CH₃)₃Al</u>	<u>(CH₃CH₂)₃Al</u>	<u>((CH₃)₂CHCH₂)₃Al</u>
 CONHCH ₂ OH	70	71	65
 CONHCH ₂ OH	81	86	88
 CONHCH ₂ OH	61 ^b	56 ^b	60 ^b
 CONHCH ₂ OH	90	81	c
	25	29	19
(CH ₃ CH ₂) ₂ NCONHCH ₂ OH	96	94	95
 CONHCH ₂ OH	76	85	40
CH ₃ CH ₂ OCONHCH ₂ OH	77	48	76

- a. Yields have not been optimized
 b. This reaction was run at room temperature
 c. This reaction gave a complex mixture of uncharacterized products

- (6) For good reviews of organoaluminum chemistry see: (a) G. Bruno, Ed., "The Use of Aluminum Alkyls in Organic Synthesis," Ethyl Corp., Baton Rouge, La., 1970; (b) T. Mole and E.A. Jeffery, "Organoaluminum Compounds," Elsevier, New York, N.Y., 1972; (c) H. Lehmkuhl, K. Ziegler and H. Gelbert, in "Methoden der Organische Chemie (Houben-Weyl)," Vol. 13/4, 4th ed., E. Muller, Ed., Georg Thieme Verlag, Stuttgart, 1970.
- (7) Four couplings which may go through a similar mechanism see: A. Meisters and T. Mole, J. Chem. Soc., Chem. Commun., 595 (1972); S. Hashimoto, Y. Kitagawa, S. Iemura, H. Yamamoto and H. Nozaki, Tetrahedron Lett., 2615 (1976).
- (8) The methylols in Table 1 were either obtained commercially or were prepared as described in reference 5a.
- (9) It is also possible that an acylimine, rather than 4, is being alkylated. Since only the lactam methylol cannot form a neutral acylimine, this might explain the low yield in this case. Another mechanism could thus be operating in the case of the lactam methylol.