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(20) Polyphosphoric acid from Matheson Coleman and Bell was used. A ratio of 1:10 of the reactants to PPA gave the best results. In a few cases (6–10) the reaction proceeded at room temperature itself and heating only led to darkening of the product.

N-Methylation of Amides, Lactams, and Ureas

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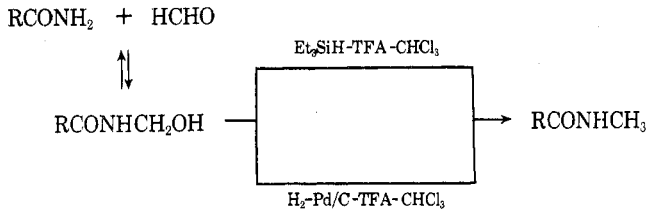
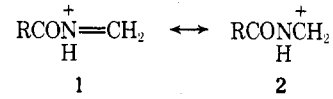
Few satisfactory methods are currently available for the N-methylation of amides and related compounds.[2] One of the more promising existing methods for amide alkylation was reported by Johnson and Crosby,[2c] who reduced a mixture of a primary amide and an acetal by catalytic hydrogenation in the presence of concentrated sulfuric acid. We now describe a milder and more versatile two-step procedure which consistently affords high isolated yields of mono-N-methylated products from the corresponding unsubstituted compounds.

Scheme I



It is well known[3] that various amides and related compounds react reversibly with formaldehyde, usually at neutral or slightly basic pH, to produce methylol derivatives (Scheme I). The equilibrium for this reaction lies to the methylol side at most pH's to the extent of about 5 kcal/mol. Many such methylols have been reported and usually are easily prepared and isolated. These methylols have found wide synthetic use in amidomethylation at carbon.[3] We have discovered that methylols derived from amides are reduced to the corresponding N-methylated product, usually at room temperature, by triethylsilane–trifluoroacetic acid, as well as by catalytic hydrogenation at atmospheric pressure in the presence of trifluoroacetic acid. A number of representative examples are shown in Table I.

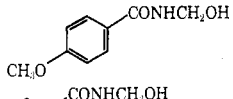
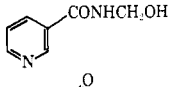
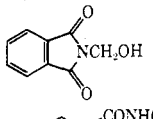
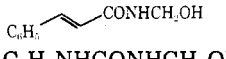
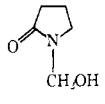
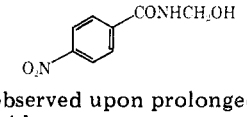
Triethylsilane has previously been shown to be effective for the reduction of many types of electrophilic species, particularly carbonium ions.[4] Treatment of an amide methylol with trifluoroacetic acid presumably produces an electrophilic acyliminium ion (**1** ↔ **2**)[3] which is then reduced to



1 **2**

the *N*-methyl compound by hydride transfer from silicon to carbon. It is likely that the catalytic reduction route, also utilizing trifluoroacetic acid, proceeds via the same acyliminium ion (**1** ↔ **2**).

Table I
Reduction of Methylols to *N*-Methyl Compounds

Registry no.	Methylol	Isolated yield of N-methylated product, %	
		Et_3SiH–TFA	H_2–5% Pd/C–TFA
57428-71-4	$C_5H_{11}CONHCH_2OH$	86	97
6282-02-6	$C_6H_5CONHCH_2OH$	94	97
57428-72-5		91	84
3569-99-1		88	93
118-29-6		No reaction[a]	No reaction
6043-65-8		85	79[b]
20779-63-9	$C_6H_5NHCONHCH_2OH$	85	80
57428-73-6	$(CH_3CH_2)_2NCONHCH_2OH$	57	65
15438-71-8		84	84
40478-12-4		92	66[c]

[a] No reduction product was observed upon prolonged heating. [b] The product is *N*-methylhydrocinnamamide. [c] The product is *p*-amino-*N*-methylbenzamide.

The catalytic hydrogenation method and the silane method complement each other nicely. Both procedures will provide *N*-methylamide from the corresponding methylol in excellent yield, but show different selectivities toward other functional groups in the same molecule.[4,5] This selectivity is exemplified by the reduction of cinnamamide methylol and *p*-nitrobenzamide methylol to different sets of products as shown in Table I. Both of these reduction methods can be used for lactam methylation as exemplified by reduction of *N*-methylolpyrrolidone to *N*-methylpyrrolidone. Imide methylols, on the other hand, appear to be inert to reduction, and phthalimide methylol was recovered unchanged in both experiments. This lack of reactivity is probably due to the inability of phthalamide methylol to form the corresponding less stable acylimidinium ion in trifluoroacetic acid.[6] Ureas can also be successfully methylated in this fashion, and in the two cases attempted (Table I) satisfactory yields were obtained using both reduction procedures.

Experimental Section

All methylols used in this study were prepared from the amide, urea, or lactam and 40% aqueous formaldehyde solution usually in the presence of potassium carbonate or sodium hydroxide using standard procedures previously described in detail.[3] Pyrrolidone methylol was purchased from K and K Laboratories. Trifluoroacetic acid was distilled from concentrated sulfuric acid before use.

General Procedure for Reduction of Methylols with Triethylsilane–Trifluoroacetic Acid. A solution containing 1 mmol of methylol, 1.14 g (10 mmol) of trifluoroacetic acid, 0.174 (1.5 mmol) of triethylsilane, and 10 ml of reagent grade chloroform was stirred for 1–4 hr at room temperature.[7] The mixture was diluted with ethyl acetate and washed with sodium bicarbonate solution. The organic phase was dried ($MgSO_4$) and evaporated to dryness, giving a nearly pure product which could be recrystallized or distilled if desired.

General Procedure for the Reduction of Methylols with Hydrogen–Pd/C–Trifluoroacetic Acid. A solution of 2 mmol of methylol, 2.28 g (20 mmol) of trifluoroacetic acid, and 200 mg of 5% Pd/C in 30 ml of reagent grade chlorofrrm was hydrogenated at room temperature and atmospheric pressure until the theoretical amount of hydrogen was absorbed. The catalyst was removed by filtration and the organic phase was washed with saturated sodium chloride solution, washed with 15% sodium carbonate solution, dried ($MgSO_4$), and evaporated to afford an essentially pure product which could be purified further if desired.

Acknowledgment. We are indebted to the National Science Foundation (MPS 75-01558), National Institutes of Health (CA12568 and HL18450), and Eli Lilly & Co. for financial support.

Registry No.—Trifluoroacetic acid, 76-05-1; triethylsilane, 617-86-7; *N*-methylhexanamide, 3418-05-1; *N*-methylbenzamide, 613-93-4; 4-methoxy-*N*-methylbenzamide, 3400-22-4; *N*-methyl-3-pyridinecarboxamide, 114-33-0; *N*-methylhydrocinnamamide, 940-43-2; *N*-methyl-*N'*-phenylurea, 1007-36-9; *N,N*-diethyl-*N'*-methylurea, 39499-81-5; *N*-methylpyrrolidone, 872-50-4; *p*-amino-*N*-methylbenzamide, 6274-22-2.

References and Notes

(1) (a) Postdoctoral Research Associate. (b) Fellow of the Alfred P. Sloan Foundation 1975–1977; recipient of an NIH Research Career Development Award, 1975–1980.
(2) (a) I. T. Harrison and S. Harrison, "Compendium of Organic Synthetic Methods", Vol. I, Wiley-Interscience, New York, N.Y., 1971, pp 211–212; (b) L. Bernardi, R. DeCastiglione, and U. Scarponi, *J. Chem. Soc., Chem. Commun.*, 320 (1975); (c) H. E. Johnson and D. G. Crosby, *J. Org. Chem.*, **27**, 2205 (1962).
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(6) It has been shown that imide methylols will undergo amidomethylation at carbon if concentrated sulfuric acid is used as catalyst.[3]
(7) In the case of nicotinamide methylol, it was found best to reflux the reaction mixture for 2 hr.

Synthetic Applications of Phenylthio[(α-diethoxymethyl)vinyl]cuprate and (α-Diethoxymethyl)vinylcopper

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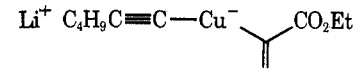
The utility of alkyl, alkenyl, and aryl organocuprate(I) reagents for the formation of carbon–carbon σ bonds via conjugate addition to α,β-unsaturated carbonyl compounds[2] and homoconjugate addition to cyclopropyl carbonyl compounds[3] has been demonstrated. Organocuprate (I) reagents have also been effectively used for selective substitution reactions with a wide variety of substrates[4]. Recently Marino[5] reported the preparation of α-carbethoxyvinylcuprate **1**, which is specific for allyl halides. Alkyl



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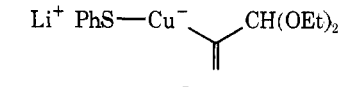
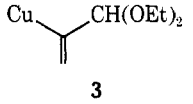


2

iodides, iodobenzene, 2-bromopropene, and benzyl bromide were unaffected under the reaction conditions employed with allyl halides. Furthermore, in direct contrast with lithium divinylcuprate, dialkylcuprates,[2] and mixed cuprate reagents,[6] the reaction of **1** with a series of α,β-unsaturated carbonyl compounds resulted in 1,2 addition to the carbonyl with the exception of methyl vinyl ketone.[7,8] In conjunction with our interest in functionalized nonterminal vinylcopper reagents,[9,10] we wish to communicate our results involving the mixed cuprate phenylthio[(α-diethoxymethyl)vinyl]cuprate (**2**) and (α-diethoxymethyl)vinylcopper (**3**).



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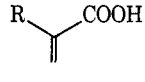
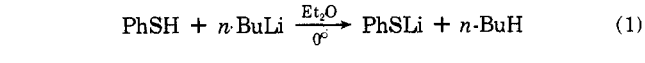


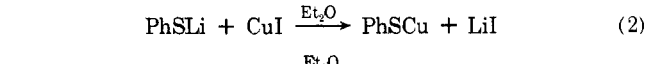
4

Our interest in reagents of type **2** stemmed from a need to construct a three-carbon unit fused to a carbon framework which would be equivalent to a 2-substituted propenoic acid derivative (e.g., **4**). In this regard we wish to report the generation of the mixed organocuprate reagent **2**, its reactivity toward allylic halides and α,β-unsaturated ketones, and its application to the synthesis of α-methylene lactones. In addition generation of the vinylcopper reagent **3** and its reactivity toward allylic halides is reported.

The mixed cuprate **2** was prepared according to eq 1–3. Thiophenol in anhydrous ether was treated with 1 equiv of



(1)



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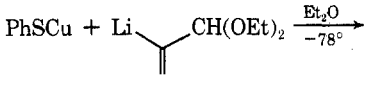

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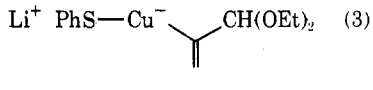

(3)

n-butyllithium. Addition of the lithium thiophenoxide to a suspension of cuprous iodide at room temperature in anhy-