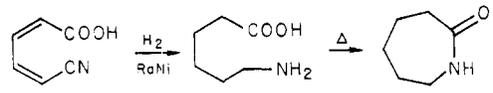
sequential two-electron processes.[12] Third, the success with both pyridine and aqueous ammonia as solvents indicates that the nature of the solvent system may not be critical,[13] provided that it is capable of effective solvation of both copper(II) and copper(I) species.[14]

Finally, in accordance with our overall objective,[2,3,15] hydrogenation of *cis,cis*-muconic acid mononitrile (**1a**) over Ra/Ni in ethanol at room temperature and under 1000 psi of hydrogen provided the ω-aminocaproic acid, which was readily converted to caprolactam[16] (eq 6).



(6)

1a

Acknowledgment. We thank Messrs. Bruce Van Buskirk, John Rodler, and Francis Ruggiero for their valuable assistance in all phases of this work. We are also indebted to the staff of our Chemical Physics Department for their analytical services.

Registry No. 1a, 73824-86-9; **1b**, 73824-87-0; **1c**, 73824-88-1; **1d**, 73824-89-2; 4-*tert*-butylcatechol, 98-29-3; 4-*tert*-butyl-1,2-benzoquinone, 1129-21-1; catecho, 120-80-9; phenol, 108-95-2; CuO, 1317-38-0; NH_3, 7664-41-7.

(11) W. Brackman and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, 74, 937, 1021, 1070, 1100, 1107 (1955).

(12) For a discussion of the possible single-step two-electron oxidation mechanisms in similar transformations, see ref 2 and 3.

(13) Other solvents including *N,N*-dimethylformamide and *N*-methylpyrrolidone have also been successfully used in the reaction.

(14) For example, both cupric hydroxide and cuprous chloride[2,3] are insoluble in water but are quite soluble in ammonium hydroxide. Similarly, pyridine efficiently stabilizes both copper(II) oxygen species[4] and copper(I) chloride.[2,3]

(15) See, for example, (a) M. M. Rogić, J. Vitrone, and M. D. Swerdloff, *J. Am. Chem. Soc.*, 98, 4756 (1976); (b) K. P. Klein, T. R. Demmin, B. C. Oxenrider, M. M. Rogić, and M. T. Tetenbaum, *J. Org. Chem.*, 44, 275 (1979).

(16) See, for example, F. Mares and D. Sheehan, *Ind. Eng. Chem. Process Des. Dev.*, 17, 9 (1978).

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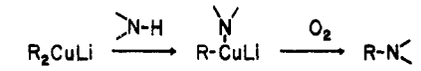
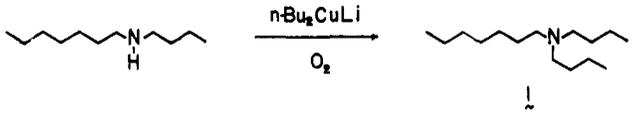
Novel *N*-Alkylation of Amines with Organocopper Reagents

Summary: A mild and efficient method for the *N*-alkylation of amines is described, based on the oxidative coupling of lithium alkylcopper amide, which is derived from lithium dialkylcuprates and primary or secondary amines. The high chemospecificity of the method was demonstrated.

Sir: There is a lack of methodologies which cleanly introduce nitrogen at donor sites.[1] The use of haloamine or hydroxyamine derivatives is a classical solution to this problem.[2] Herein we describe an entirely different approach based on the oxidative coupling of lithium alkylcopper amide,[3] which is derived in situ from lithium dialkylcuprates and primary or secondary amines.[4]



In a typical example, butylheptylamine (1 equiv in ether) was added to lithium dibutylcuprate (5 equiv in ether–hexane) at −20 °C. Stirring was continued at −20 °C for 2 h.[5] Excess molecular oxygen was bubbled into the suspension via syringe at −20 °C over 5 min. The mixture was then quenched in concentrated ammonium hydroxide and extracted with ethyl acetate. Purification by column chromatography on silica gel (*i*-$PrNH_2$–MeOH 1:200) gave dibutylheptylamine (**1**) in 73% yield.[6]

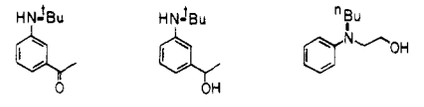


1

The conditions cited above were crucial for efficient *N*-alkylation of amines. Under similar conditions without oxygen, only a trace amount of **1** was obtained with the recovery of butylheptylamine. Ethereal solvents (diethyl ether or tetrahydrofuran (THF)) were preferable, and less polar solvents (toluene or hexane) decreased the yield.[7] The use of ether as solvent with 3 and 1 equiv of lithium dibutylcuprate afforded **1** in yields of 62 and 54%, respectively.[8]

Representative results obtained on oxidation of other alkylcopper amides are listed in Table I. The method seems to be highly effective for the oxidative coupling of amines with primary alkyl and aryl groups.[9] Furthermore, the bulky *tert*-butyl group can also be introduced by this method. Although introduction of tertiary alkyl groups gave poor yields (23–46%), the conversion yields are usually very high (94% yield[10] for *m*-(*tert*-butylamino)acetophenone (**2**)). In fact, the classical methods are totally ineffective for such transformations. For *tert*-butylation, the polar solvent system, e.g., THF, is preferable and only the starting amine was recovered in the ether solvent. In some cases (entry 1 and 5), Grignard reagents were found to give somewhat higher yields of coupling products than the corresponding organolithium compounds.

Application of the method to *m*-aminoacetophenone led to the desired *N*-alkylation product **2** without any unde-



2 (32% (94%)[10]) **3** (39%) **4** (37%)

sirable complication. Similarly, *N*-alkylation of *m*-(1-hydroxyethyl)aniline and 2-anilinoethanol was achieved successfully without any protection of the hydroxy function.[11] A darkened bond in the formula indicates the bond created by carbon–nitrogen bond forming reactions.

(1) D. Seebach, *Angew. Chem., Int. Ed. Engl.*, 18, 239 (1979).

(2) For a recent example, see D. I. C. Scopes, A. F. Kluge, and J. A. Edwards, *J. Org. Chem.*, 42, 376 (1977).

(3) For the oxidative coupling of lithium dialkylcuprates, see (a) G. M. Whitesides, J. SanFilippo, Jr., C. P. Casey, and E. J. Panek, *J. Am. Chem. Soc.*, 89, 5302 (1967); (b) G. H. Posner, *Org. React.*, 22, 253 (1975).

(4) Although we have no evidence on the formation of lithium alkylcopper amide, the following reaction infers its existence: The reaction of butylcopper with lithium butylheptylamide in the presence of excess lithium dibutylcuprate at −20 °C for 2 h gave **1** in 78% yield after oxidative workup.

(5) A total of 36.5 mL of solvent was used per millimole of organocopper reagent. All operations were performed under argon atmosphere.

(6) This compound was characterized by IR, mass, and NMR spectra.

(7) Decomposition products were formed at the origin of a TLC plate.

(8) The use of 10 equiv of *n*-Bu_2CuLi gave a yield comparable to that with 5 equiv of *n*-Bu_2CuLi.

(9) Despite much information on organocopper reactions, the available data, in our hands, are not sufficient to allow formulation of a detailed course of this reaction. However, the reactivity of the alkylcopper amide and the yield of the reaction seem to be closely dependent on the type of solvent used and on coordination phenomena of the nitrogen atom.

(10) The yield is based on consumed *m*-aminoacetophenone.

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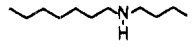
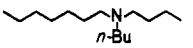
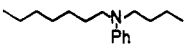
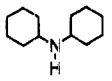
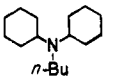
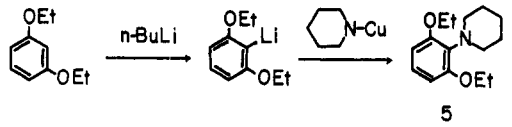
Table I. *N*-Alkylation Reaction with Organocopper Reagents

entry	amine	RLi for R_2CuLi (RMgX for RCu)	reaction condition,[a]	product	yield, %
1		*n*-BuLi	A		73
		MeLi	B		39
		MeMgCl	F		52
		PhLi	C		64
2		*n*-BuLi	A		38
3	$(PhCH_2)_2NH$	*n*-BuLi	A	$(PhCH_2)_2N$-*n*-Bu	62
		t-BuLi	D	$(PhCH_2)_2N$-*t*-Bu	26
		MeLi	B	$(PhCH_2)_2NMe$	76
4		*t*-BuLi	D		23
5	PhNHMe	*n*-BuLi	A	PhN(Me)-*n*-Bu	57
		MeLi	E	$PhNMe_2$	33
		MeMgCl	F[b]		46
		PhLi	C[c]	Ph_2NMe	72
6	Ph_2NH	PhLi	C	Ph_2NPh	94
7	$PhNH_2$	*t*-BuLi	D	PhNH-*t*-Bu	46 (42[d]) 15 (17,[d] 19[e])
8		*t*-BuLi	D		35

[a] A: Ether (−20 °C, 2 h), O_2 at −20 °C. B: Ether (25 °C, 2 h), O_2 at 25 °C. C: Ether (reflux, 6 h), O_2 at −78 °C. D: THF (−20 °C, 2 h), O_2 at −20 °C. E: Toluene (0 °C, 2 h), O_2 at −78 °C. F: THF (25 °C, 2 h), O_2 at 25 °C. G: THF-HMPA (20:1) (−20 °C, 2 h), O_2 at −20 °C. [b] Addition of HMPA (10 vol %). [c] Use of THF instead of ether. [d] Use of 1,2-dimethoxyethane (DME). [e] Use of DME-HMPA (20:1).

The introduction of amino groups to organic substrates (i.e., the reverse methodology described above) was also realized with excess copper amide. Thus, treatment of *o,o'*-diethoxyphenyllithium, derived from *m*-diethoxybenzene and *n*-butyllithium by metalation,[12] with 5 equiv of copper piperidide (from lithium piperidide and cuprous iodide)[13] in THF–hexane under reflux for 2 h followed by quenching with molecular oxygen gave *N*-(*o,o'*-diethoxyphenyl)piperidine (**5**) in 51% yield.[14] This shows that a



5

wide variety of organolithium compounds and lithium alkylamides can be efficiently coupled in the presence of cuprous iodide with the formation of a new carbon–nitrogen bond under mild conditions.[2]

Continuing studies are planned on even milder procedures utilizing other transition metals to develop the scope of this reaction.

Acknowledgment is made to the donors of the Petroleum Research Fund (10615-AC1), administered by the American Chemical Society, for partial support of this research.

Registry No. **1**, 3553-87-5; **2**, 73679-98-8; **3**, 73679-99-9; **4**, 3046-94-4; **5**, 73680-00-9; *m*-aminoacetophenone, 99-03-6; *m*-(1-hydroxyethyl)aniline, 2454-37-7; 2-anilinoethanol, 122-98-5; *o,o'*-diethoxyphenyllithium, 73680-01-0; copper piperidide, 73680-02-1; *N*-butylheptanamine, 73680-03-2; dicyclohexylamine, 101-83-7; dibenzylamine, 103-49-1; decanamine, 2016-57-1; *N*-methylbenzenamine, 100-61-8; diphenylamine, 122-39-4; benzenamine, 62-53-3; 1-naphthalenamine, 134-32-7; *N*-butyl-*N*-methylheptanamine, 73680-04-3; *N*-butyl-*N*-phenylheptanamine, 73680-05-4; *N*-butyldicyclohexylamine, 27942-54-7; *N*-butyldibenzylamine, 22014-90-0; *N*-*tert*-butyldibenzylamine, 30923-82-1; *N*-methyldibenzylamine, 102-05-6; *N*-*tert*-butyldecanamine, 73680-06-5; *N*-butyl-*N*-methylbenzenamine, 3416-49-7; *N,N*-dimethylbenzenamine, 121-69-7; *N*-methyldiphenylamine, 552-82-9; triphenylamine, 603-34-9; *N*-*tert*-butylbenzenamine, 937-33-7; *N*-*tert*-butylnaphthalenamine, 54961-92-1; lithium dibutylcuprate, 24406-16-4; lithium dimethylcuprate, 15681-48-8; methylcopper, 1184-53-8; lithium diphenylcuprate, 23402-69-9; lithium bis(1,1-dimethylethyl)cuprate, 23402-75-7.

(11) The same reaction conditions as described for the preparation of 1 were used. The compounds **2**–**4** were fully characterized by spectral data. **2**: NMR ($CDCl_3$) δ 6.76–7.42 (4 H, m, aryl H), 3.41 (1 H, s, NH), 2.51 (3 H, s, $CH_3C{=}O$), 1.37 (9 H, s, CH_3C); mass spectrum, *m/e* (%) 44 (100), 176 (57, $M^+ - 15$), 191 (23, M^+). **3**: NMR ($CDCl_3$) δ 6.47–7.31 (4 H, m, aryl H), 4.71 (1 H, q, *J* = 6.2 Hz, CHO), 3.01 (1 H, s, NH), 1.41 (3 H, d, *J* = 6.2 Hz, CH_3CO), 1.30 (9 H, s, *t*-Bu); mass spectrum, *m/e* (%) 178 (100, $M^+ - 15$), 193 (74, M^+). **4**: NMR ($CDCl_3$) δ 6.55–7.44 (5 H, m, aryl H), 3.59–3.98 (2 H, m, CH_2O), 3.06–3.59 (4 H, m, CH_2N), 2.08 (1 H, s, OH), 1.00–1.81 (4 H, br s, aliphatic CH_2), 0.94 (3 H, m, CH_3); mass spectrum, *m/e* (%) 193 (100, M^+).

(12) H. Gilman, H. B. Willis, T. H. Cook, F. J. Webb, and R. N. Meals, *J. Am. Chem. Soc.*, **62**, 667 (1940).

(13) The copper piperidide was prepared in situ by treatment of lithium piperidide with cuprous iodide in THF–hexane at 0 °C for 30 min. See also T. Tsuda, M. Miwa, and T. Saegusa, *J. Org. Chem.*, **44**, 3734 (1979).

(14) NMR ($CDCl_3$) δ 6.34–7.30 (3 H, m, aryl H), 4.01 (4 H, q, *J* = 7 Hz, CH_2O), 3.07 (4 H, br s, CH_2N), 1.58 (6 H, br s, aliphatic CH_2), 1.40 (6 H, t, *J* = 7 Hz, CH_3); mass spectrum, *m/e* (%) 220 (74, $M^+ - 29$), 249 (100, M^+).

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