(*R,S*)-6-chloro-9-[1-(2-hydroxyethoxy)ethyl]purine (**2a**)[12] and (*R,S*)-9-[3-benzyloxy-1-(2-hydroxyethoxy)propyl]-6-chloropurine (**2c**).[13]

The substituted chloropurines were treated with methanolic ammonia at 110 °C in a sealed tube for 18 h to generate the corresponding acyclic adenosine analogues **1a**, **3b**, and **3c** in 80–90% yield.[14-16] The debenzylation of **3b** and **3c** was done according to the general procedure of Broom et al. and provided essentially quantitative conversion to compounds **1b** and **1c**.[17-19]

The ready availability of substituted dioxolanes and the excellent alkylating properties demonstrated by the derived iodoalkyl (trimethylsilyloxy)ethyl ethers make this an attractive synthetic methodology. In addition, our preparation now offers the possibility of synthesizing a variety of specifically substituted compounds, many of which would be quite difficult to obtain by conventional methods.

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Registry No. **1a**, 71516-41-1; **1b**, 71564-04-0; **1c**, 71516-42-2; **2a**, 71516-43-3; **2b**, 71516-44-4; **2c**, 71516-45-5; **3b**, 71516-46-6; **3c**, 71516-47-7; 2-methyl-1,3-dioxolane, 497-26-7; 2-(benzyloxymethyl)-1,3-dioxolane, 71516-48-8; 2-(2-benzyloxyethyl)-1,3-dioxolane, 71516-49-9; 6-chloropurine, 87-42-3; trimethylsilyl iodide, 16029-98-4.

Supplementary Material Available: Experimental details for the preparation of the compounds described in this paper (6 pages). Ordering information is given on any current masthead page.

(11) Only representative spectral data are provided to identify the compounds described. Microanalyses determined for C, H, N for all compounds are correct to within 0.4% of the calculated values.

(12) Compound **2a**: mp 89.5–90 °C; NMR ($CDCl_3$) δ 1.88 (d, J = 6 Hz, 3, CH_3), 2.39 (br s, 1, OH), 3.3–3.9 (m, 4, OCH_2), 6.09 (q, J = 6 Hz, 1, NCHO), 8.35 (s, 1, purine CH), 8.73 (s, 1, purine CH).

(13) Compound **2c**: mp 79.5–80.5 °C; NMR ($CDCl_3$) δ 2.25–2.65 (m, 2, $CHCH_2$), 3.25–3.85 (m, 6, OCH_2), 4.42 (s, 2, CH_2Ph), 6.08 (t, J = 7.5 Hz, 1, NCHO), 7.28 (s, 5, ArH), 8.24 (s, 1, purine CH), 8.72 (s, 1, purine CH).

(14) Compound **1a**: mp 147.5–148.5 °C; NMR ($(CD_3)_2SO$) δ 1.71 (d, J = 6 Hz, 3, CH_3), 3.2–3.5 (m, 4, OCH_2), 4.53 (br, 1, NH or OH), 5.83 (q, J = 6 Hz, 1, NCHO), 7.15 (s, 2, NH or OH), 8.08 (s, 1, purine CH), 8.25 (s, 1, purine CH).

(15) Compound **3b**: NMR ($CDCl_3$) δ 2.75 (br, 1, NH or OH), 3.5–3.85 (m, 4, OCH_2CH_2O), 3.93 (d, J = 6 Hz, 2, OCH_2), 4.55 (s, 2, CH_2Ph), 5.90 (br, 2, NH or OH), 5.94 (t, J = 6 Hz, 1, NCHO), 7.25 (s, 5, ArH), 7.98 (s, 1, purine CH), 8.31 (s, 1, purine CH).

(16) Compound **3c**: mp 134–135 °C; NMR (CD_3OD) δ 2.33–2.61 (m, 2, $CHCH_2$), 3.33–3.73 (m, 6, OCH_2), 4.36 (s, 2, CH_2Ph), 5.97 (t, J = 6 Hz, 1, NCHO), 7.20 (s, 5, ArH), 8.19 (s, 1, purine CH), 8.23 (s, 1, purine CH).

(17) Christensen, L. F.; Broom, A. D. *J. Org. Chem.* **1972**, *37*, 3398.

(18) Compound **1b**: NMR ($(CD_3)_2SO$) δ 3.20–3.65 (m, 4, OCH_2CH_2O), 3.89 (d, J = 6 Hz, 2, OCH_2), 5.77 (t, J = 6 Hz, 1, NCHO), 7.27 (br, 1, NH or OH), 8.13 (s, 1, purine CH), 8.24 (s, 1, purine CH).

(19) Compound **1c**: NMR ($(CD_3)_2SO$) δ 2.10–2.40 (m, 2, $CHCH_2$), 3.25–3.60 (m, 6, OCH_2), 4.57 (br, 2, NH or OH), 5.85 (t, J = 6 Hz, 1, NCHO), 7.19 (br, 2, NH or OH), 8.13 (s, 1, purine CH), 8.28 (s, 1, purine CH).

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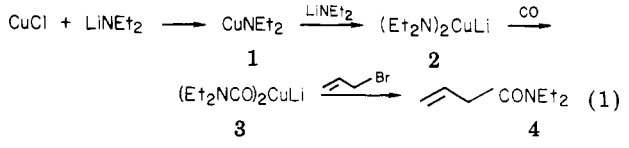
Lithium Bis(*N,N*-diethylcarbamoyl)cuprate. A Reagent for Direct Carbamoylation

Summary: Thermally stable lithium bis(*N,N*-diethylcarbamoyl)cuprate, which was readily prepared from CO and lithium bis(*N,N*-diethylamino)cuprate, was effective for direct carbamoylation.

Sir: Introduction of a carbonyl functionality into an organic compound is a useful interconversion reaction in organic synthesis. For example, several acyllithium equivalent reagents have been developed for the introduction of an acyl group because of the inaccessibility of acyllithium.[1] Here we report lithium bis(*N,N*-diethylcarbamoyl)cuprate, $(Et_2NCO)_2CuLi$ (**3**), as a useful reagent for direct carbamoylation.



The following procedures were carried out under nitrogen. An equimolar reaction of CuCl and $LiNEt_2$ in a mixed solvent of tetrahydrofuran (THF) and hexamethylphosphoric triamide (HMPA) (4:1) at −20 °C produced a precipitate of $CuNEt_2$ (**1**), which was dissolved by an additional 1 equiv of $LiNEt_2$ to form an homogeneous solution. This solution absorbed 2 equiv of carbon monoxide under ordinary pressure at ambient temperature. Treatment of the resulting solution with allyl bromide gave *N,N*-diethyl 3-butenamide (**4**) in 45% yield based on $LiNEt_2$ with concomitant evolution of CO nearly equivalent to copper. The same reaction under CO pressure of 50 kg/cm^2 produced **4** in 76% yield. These results may be reasonably interpreted by the intermediacy of bis(*N,N*-diethylcarbamoyl)cuprate (**3**) generated from the CO insertion into bis(*N,N*-diethylamino)cuprate (**2**) (eq 1). The CO absorption by **2** contrasts in a striking way with the inertness of **1** toward CO at ambient temperature. Similarly, lithium bis(carbamoyl)cuprate derived from morpholine gave the corresponding 3-butenamide in 93% yield based on $LiNCH_2CH_2OCH_2CH_2$ under CO of 50 kg/cm^2. The formation of **3** and its trapping by allyl bromide at ambient temperature are interesting compared to the behavior of $LiNEt_2$ toward CO. $LiNEt_2$ prepared from $HNEt_2$ and *n*-BuLi absorbed an equimolar amount of CO at −78 °C in THF–HMPA (4:1). However, the treatment of the resulting solution with allyl bromide did not produce **4**, which suggests that *N,N*-diethylcarbamoyllithium cannot exist even at −78 °C probably due to its facile self-condensation.[2]

In the following experiments, **3** was prepared under CO pressure of 50 kg/cm^2. Heating the solution of **3** after the purge of the compressed CO gas at 60 °C for 2 h followed by the addition of allyl bromide did not give **4**, which indicates the decomposition of **3**. On the other hand, heating the solution of **3** at 60 °C for 2 h under CO pressure of 50 kg/cm^2 produced **4** in 64% yield by the treatment with allyl bromide. Similar reactions under CO pressure at 80 and 100 °C showed that **3** was thermally

(1) D. Seebach and K. H. Geiss in "New Applications of Organometallic Reagents in Organic Synthesis", D. Seyferth, Ed., Elsevier, Amsterdam, The Netherlands, 1976, pp 1–92.

(2) Sterically hindered *N,N*-diisopropylcarbamoyllithium generated from the reaction of lithium *N,N*-diisopropylamide and CO can exist at −78 °C; V. Rautenstrauch and M. Joyeux, *Angew. Chem., Int. Ed. Engl.*, 18, 83 (1979).

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Table I. Formations of Lithium Bis(carbamoyl)cuprates and Their Reactions with Allyl Bromide

$$(R^1R^2N)_2CuLi \xrightarrow[THF\text{-}HMPA]{CO} (R^1R^2NCO)_2CuLi \xrightarrow[rt,\ 2\ h]{\sim\!\!\sim Br^b} \sim\!\!\sim CONR^1R^2$$

		formations of $(R^1R^2NCO)_2CuLi$			% yields of $\sim\!\!\sim CONR^1R^2$[a]
R^1	R^2	CO, kg/cm²	temp, °C	time, h	
Et	Et	1	rt	12	45
Et	Et	50	rt	12	76
Et	Et	1[c]	60	2	0
Et	Et	50	60	2	64
Et	Et	50	80	1.5	67
Et	Et	50	100	1.5	39
$-(CH_2)_2O(CH_2)_2-$		1	rt	12	47
$-(CH_2)_2O(CH_2)_2-$		50	rt	12	93
n-Bu	H	50	rt	12	22
Ph	H	50	rt	12	28

[a] The yield was based on $LiNR^1R^2$. [b] The reaction of allyl bromide with lithium bis(carbamoyl)cuprate generated under CO pressure of 50 mg/cm² was carried out after the purge of the compressed CO gas. [c] 3 prepared under CO pressure of 50 kg/cm² at room temperature was heated at 60 °C after the purge of the compressed CO gas.

Table II. Reactions of 3 with Organic Halides[d]

$$(Et_2NCO)_2CuLi \xrightarrow{RX} RCONEt_2$$

run	RX	temp, °C[b]	time, h	% $RCONEt_2$[a]
1	MeI	80	1	10
2	PhI	80	2	49
3	PhCH=CHBr	60	0.5	trace
4	MeCOBr	−78 → rt[c]	1 → 0.5[c]	70
5	MeCOBr	80	1	65
6	PhCOBr	−78 → rt[c]	1 → 0.5[c]	64
7	PhCOBr	60	1	74
8	PhCOCl	−78 → rt[c]	1 → 0.5[c]	23
9	PhCOCl	80	0.5	61
10	EtOCOCl	60	1	36

[a] The yield was based on $LiNEt_2$. [b] The reaction above room temperature was carried out under CO pressure of 50 kg/cm². [c] After the reaction of 3 with acid halide at −78 °C for 1 h, the resulting mixture was allowed to stand at room temperature for 0.5 h. [d] In runs 5-9, amides, $RNEt_2$, were formed as byproducts in 10-20% yields.

stable at 80 °C, but decomposed partly at 100 °C (Table I). Insertion reactions of CO into several copper complexes[3] involving the Cu–C, Cu–O, and Cu–N bonds have been reported to cause the coupling of the ligands, but there is no precedent for the intermediate formation of a stable CO-incorporated copper complex which can be utilized for the further organic reaction. Formations of the corresponding carbamoylcopper complexes derived from *n*-$BuNH_2$ and $PhNH_2$ were examined, but the results were not as satisfactory as those of **3** (Table I).[4]

The results of the reactions of **3** with various organic halides are summarized in Table II. The reactions with acid bromides took place smoothly under mild conditions to produce α-keto amides. The reaction of a less reactive acid chloride was satisfactorily carried out at a higher reaction temperature. The reaction of **3** with acid halide provides a convenient method for the synthesis of α-keto acid, for which existing methods are often laborious. Several reagents for direct carbamoylation have been reported.[2,5] Lithium *N,N*-dimethylcarbamoylnickel carbonylate,[5f] which is effective for the carbamoylation of vinylic and aromatic halides, reacts with acid halides to produce the corresponding amides with concomitant decarbonylation instead of α-keto amides. *N,N*-Diisopropylcarbamoyllithium is easily formed at low reaction temperatures of −78 to −95 °C by the metalation of *N,N*-diisopropylformamide[5c,5e] or the CO insertion into lithium *N,N*-diisopropylamide.[2] *N,N*-Dimethylcarbamoyllithium is generated in the presence of reacting carbonyl compounds by the metalation of *N,N*-dimethylformamide at −78 °C.[5b] However, their reaction with an acid halide has not been reported.[5a] **3** did not react with benzaldehyde or ethyl benzoate, which contrasts with the high reactivity of *N,N*-dialkylcarbamoyllithiums toward carbonyl groups.[5b-5e]

3 underwent a conjugate addition to methyl vinyl ketone (MVK). An equimolar reaction of **3** with MVK in THF–HMPA (4:1) at −78 °C gave *N,N*-diethyllevulinamide in 38% yield based on MVK after a usual workup (eq 2). Use of an excess of **3** to MVK, Cu/MVK = 4, gave

$$(Et_2NCO)_2CuLi + CH_2{=}CHCOCH_3 \xrightarrow[THF\text{-}HMPA]{-78\ °C,\ 1\ h} \xrightarrow{H_3O^+} Et_2NCOCH_2CH_2COCH_3 \quad (2)$$

the adduct in 78% yield. To our knowledge, this is the first example of direct introduction of a carbonyl group by the conjugate addition of lithium organocuprate. The reaction of **3** with cyclohexenone, however, was not successful.

The change of the reactivity of **3** may be expected when the carbamoyl group of **3** is transferred to other metals. The carbamoylation of β-bromostyrene with **3** did not take place. Interestingly, however, in the presence of 10 mol % $Ni(OAc)_2$, the reaction produced *N,N*-diethylcinnamide in 51% yield based on $LiNEt_2$. The transmetalation reaction using **3** may be expected to enlarge the scope of its carbamoylation reactions.

Registry No. **1**, 71426-07-8; **2**, 71426-08-9; **3**, 71435-48-8; **4**, 17093-17-3; $[((CH_2)_2O(CH_2)_2)N]_2CuLi$, 71426-09-0; (*n*-BuNH)$_2$CuLi, 71426-10-3; $(PhNH)_2CuLi$, 71426-11-4; $[((CH_2)_2O(CH_2)_2)NCO]_2CuLi$, 71435-45-5; (*n*-BuNHCO)$_2$CuLi, 71435-46-6; $(PhNHCO)_2CuLi$, 71435-47-7; $CH_2{=}CHCH_2N((CH_2)_2O(CH_2)_2)$, 696-57-1; $CH_2{=}$

(3) (a) T. Saegusa and T. Tsuda in "New Synthetic Reaction by Metal Complexes (in Japanese)", S. Otsuka, Ed., Nankodo, Tokyo, Japan, 1970, pp 74–92; (b) J. Schwartz. *Tetrahedron Lett.*, 2803 (1972); (c) T. Saegusa, T. Tsuda, and K. Isayama, *J. Org. Chem.*, **35**, 2976 (1970); (d) T. Saegusa, T. Tsuda, K. Nishijima, and K. Isayama, *Tetrahedron Lett.*, 3379 (1968).

(4) Rapid rearrangement of *N-tert*-butylcarbamoyllithium to *N*-lithio-*N-tert*-butylformamide has been reported: V. Rautenstrauch and M. Joyeux, *Angew. Chem., Int. Ed. Engl.*, 18, 85 (1979).

(5) (a) U. Schöllkopf and F. Gerhart, *Angew. Chem., Int. Ed. Engl.*, **6**, 805 (1967); (b) B. Bănhidai and U. Schöllkopf, *ibid.*, **12**, 836 (1973); (c) R. R. Fraser and P. R. Hubert, *Can. J. Chem.*, **52**, 185 (1974); (d) U. Schöllkopf and H. Beckhaus, *Angew. Chem., Int. Ed. Engl.*, **15**, 293 (1976); (e) A. S. Fletcher, K. Smith, and K. Swaminathan, *J. Chem. Soc., Perkin Trans. 1*, 1881 (1977); (f) S. Fukuoka, M. Ryang, and S. Tsutsumi, *J. Org. Chem.*, **36**, 2721 (1971).

$CHCH_2NH$-*n*-Bu, 4538-09-4; CH_2=$CHCH_2NHPh$, 589-09-3; MeI, 74-88-4; PhI, 591-50-4; PhCH=CHBr, 103-64-0; MeCOBr, 506-96-7; PhCOBr, 618-32-6; PhCOCl, 98-88-4; EtOCOCl, 541-41-3; $MeCONEt_2$, 685-91-6; $PhCONEt_2$, 1696-17-9; PhCH=$CHCONEt_2$, 3680-04-4; $MeCOCONEt_2$, 22381-21-1; $PhCOCONEt_2$, 34906-86-0; $EtOCOCONEt_2$, 5411-58-5; CO, 630-08-0; $LiNEt_2$, 816-43-3; CH_2=$CHCH_2Br$, 106-95-6.

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Photooxidation of Dimethylthymine: Contrasting Regio- and Stereospecific Reactions of the Initial Photoproduct with Nucleophiles

Summary: Postirradiation treatment of photooxidized 1,3-dimethylthymine with phenol resulted in the formation of the unexpected carbon–carbon coupling products, *cis*-5-hydroxy-6-[*p*- or *o*-hydroxyphenyl]-1,3-dimethyl-5,6-dihydrothymine (**6a** and **6b**), rather than the anticipated 6-phenoxy adduct analogous to the products observed with other oxygen and sulfur nucleophiles, thus indicating two different mechanistic pathways for ring opening of the initial epoxide which may be of significance in chemical reactions of biological importance.

Sir: Recently, we reported the preliminary study of photooxidation of pyrimidines (**1a,b**)[1] using α-diketones (**2a,b**) as sensitizers.[2] The results suggest the formation of highly reactive pyrimidine 5,6-epoxides (**3**) as intermediates[1] (Scheme I). Subsequently, studies of the reactions of *trans*-5-bromo-6-hydroxy-5,6-dihydrothymines with nucleophiles in the presence of bases provide more definitive evidence for the formation of **3**.[3] **3** is attacked readily by nucleophiles to give adducts which in one case were shown to be primarily of cis configuration.[1] In this communication we establish conclusively the structures and configurations of three adducts which are indicative of *two different mechanistic pathways depending on the nature of the nucleophile.* Postirradiation treatment of photooxidized[4] dimethylthymine (**1a**) with water, acetic acid, or thiophenol as nucleophiles gave exclusively the cis adducts **5a–c** in the yields indicated, with no evidence for the presence of a trans isomer in any case.[5] Glycol **5a** and its trans isomer have been independently synthesized,[6] and **5b** was shown to be cis by its facile hydrolysis to **5a** on a silica gel plate. Since stereochemistry of 5,6-dihydropyrimidines cannot be assigned on the basis of ^1H NMR chemical shifts alone, even when both isomers are available, a single-crystal X-ray diffraction analysis of **5c** was performed (see below).

In contrast, postirradiation treatment of photooxidized **1a** with phenol gave (80% yield) a 3:2 mixture of two isomeric adducts which we suggested initially were *cis*- and *trans*-5-hydroxy-6-phenoxy-1,3-dimethyl-5,6-dihydrothymines. However, reexamination of the 100-MHz ^1H-NMR spectrum of the major isomer (mp 204 °C) showed that, in addition to the previously described[1] broad singlet at δ 8.18 originally attributed to C-5 **OH**, a second broad singlet at δ 3.92 can be seen, and the integral of the multiplet at δ 6.80 corresponded more closely to 4 H than to 5 H. A single-crystal X-ray diffraction analysis (see below) confirmed that the major isomer was the unexpected carbon–carbon coupling product **6a** and established its configuration as cis. The minor isomer, obtained initially as a viscous oil, crystallized slowly and was purified by recrystallization from benzene, mp 175 °C. Its NMR spectrum, unlike that of the major isomer, did not reveal a clue as to its identity. Singlets for the C-5 CH_3, the two N-CH_3 groups, and C-6 H at δ 1.71, 3.06, 3.27, and 4.71, respectively, and a multiplet at δ 6.63–7.20 integrating for 4–5 H were the only signals observed. However, its identity as the *o*-hydroxy adduct **6b**, also of cis configuration, was established by X-ray diffraction analysis. No other isomeric adduct was detected.

Table I

compound	**5c**	**6a**	**6b**
crystal class	monoclinic	monoclinic	monoclinic
space group	$P2_1/n$	$P2_1/c$	$P2_1/c$
a, Å	11.100 (3)	13.056 (4)	8.363 (3)
b, Å	11.326 (3)	8.317 (3)	12.434 (4)
c, Å	11.026 (3)	13.478 (6)	12.406 (5)
β, degrees	96.2 (1)	117.4 (1)	103.6 (1)
Z	4	4	4
radiation	Cu Kα	Cu Kα	Mo Kα

Pertinent physical constants, derived from the X-ray work, for the crystals of **5c**, **6a**, and **6b** are given in Table I. All three structures were solved by the symbolic addition procedure for centrosymmetric crystals.[7] The results are displayed in the stereodiagrams[8] in Figure 1. In all three compounds the heterocyclic ring has five coplanar atoms (±0.1 Å) and the sixth atom C-6 in **5c** and **6b** and C-5 in **6a** lies approximately 0.6 Å from the plane. In **5c** the sulfur atom forms a bridge between the two rings which are almost parallel to one another. In **6a** and **6b** the two rings are essentially perpendicular to one another.

In the initial work prior to the structural determinations of the phenol adducts it was apparent that, if a pyrimidine 5,6-epoxide was indeed an intermediate photoproduct, it did not undergo S_N2 attack by nucleophiles to give trans products. To account for the predominance or exclusive formation of cis products, we had envisioned this as one of the electronegatively substituted systems where gauche interactions[9] are important and the epoxide intermediate is sufficiently stabilized by zwitterionic contributions to allow nucleophilic attack from an energetically favored direction giving cis adducts.[1] The cis carbon–carbon bonded phenol adducts may be regarded as products of electrophilic attack at the ortho and para positions of phenol, but the possibility of a radical coupling mechanism[10] cannot be excluded.

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(2) N. Shimizu and P. D. Bartlett, *J. Am. Chem. Soc.*, **98**, 4193 (1976).
(3) H.-S. Ryang and S. Y. Wang, *J. Org. Chem.*, **44**, 1191 (1979).
(4) Experimental conditions for the photooxidations are given in ref 1, footnote 5.
(5) Reaction products were separated by preparative TLC on silica gel with 3:2 $CHCl_3/CH_3CN$ as eluent.
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