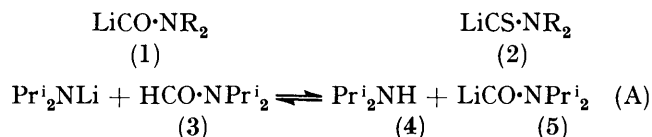


Generation of Di-isopropylcarbamoyl-lithium from *NN*-Di-isopropylformamide and *t*-Butyl-lithium. Syntheses of α -Hydroxy- and α -Oxo-amides¹

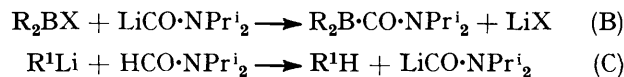
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Detailed investigations of reaction conditions for optimum formation of di-isopropylcarbamoyl-lithium from *NN*-di-isopropylformamide and organolithium reagents have led to the development of a nearly quantitative procedure, using *t*-butyl-lithium in diethyl ether–tetrahydrofuran–pentane (4 : 4 : 1) at -95°C . The species so formed reacts with electrophiles such as aldehydes, ketones, esters, and D_2O to give high yields of the expected products. Less reactive electrophiles such as alkyl iodides also react, but yields are lower and these reactions are of little synthetic significance. Benzyl bromide is sufficiently reactive, but the initial product is acidic, so that deprotonation and further alkylation occur.

SYNTHETIC applications of carbonyl anion equivalents are well known and well documented.² Experimental steps would be saved if carbonyl anions could be generated directly. Unfortunately, however, such anions derived from simple aldehydes have so far defied useful synthesis. On the other hand, lithium species of types (1)³ and (2)⁴ are known, and can be formed in high yield by the reaction of lithium di-isopropylamide with the appropriate formamide or thioformamide at low temperature [*e.g.* reaction (A)].



We were interested in species of type (1) as possible reagents for the synthesis of acylboron compounds⁵ according to reaction (B), but preliminary experiments with the carbamoyl-lithium species (5) prepared by reaction (A) were not encouraging. It seemed likely that the presence of the amine (4) might be responsible for some of the problems, and so we sought a synthesis of (5) in which this by-product would not be formed. Despite some discouraging statements in the literature^{3b} we have investigated the reactions of di-isopropylformamide (3)



† For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1976, Index issue.

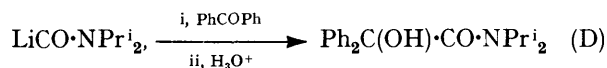
‡ There may be confusion over the proportions of the component solvents in Trapp's mixture, because different original papers by Köbrich and Trapp refer to different proportions. Here we refer specifically to the 4 : 4 : 1 mixture.

¹ Preliminary communication, K. Smith and K. Swaminathan, *J.C.S. Chem. Comm.*, 1976, 387.

with organolithium reagents [reaction (C)]; our studies reveal that such a process is indeed possible under controlled conditions.

RESULTS AND DISCUSSION

As a means of estimation of the extent of production of the carbamoyl-lithium (5) under a given set of conditions, the product (6) of its reaction with benzophenone [reaction (D)] was isolated by column chromatography. Under conditions similar to those described in the literature^{3c} for reaction (A), it was observed that, of the reagents tried (MeLi, PhLi, and Bu^tLi), only Bu^tLi gave a significant yield (20%) of (6). This reagent was therefore studied further, particularly with different solvents and reaction conditions. Full details of these studies are given in Supplementary Publication No. SUP 22084 (12 pp.);† a few of the results are recorded in Table 1.



The solvent mixtures found to be most suitable in the present study are exactly those, *viz.* diethyl ether–tetrahydrofuran (80 : 20) and Trapp's mixture,‡ which have proved effective for other deprotonation reactions

² For recent reviews see D. Seebach and M. Kolb, *Chem. and Ind.*, 1974, 687; O. W. Lever, *Tetrahedron*, 1976, **32**, 1943.

³ (a) U. Schöllkopf and H. Beckhaus, *Angew. Chem.*, 1976, **88**, 296; (b) B. Bánhidai and U. Schöllkopf, *Angew. Chem. Internat. Edn.*, 1973, **12**, 836; (c) R. R. Fraser and P. R. Hubert, *Canad. J. Chem.*, 1974, **52**, 185.

⁴ D. Enders and D. Seebach, *Angew. Chem. Internat. Edn.*, 1973, **12**, 1014; D. Seebach, W. Lubosch, and D. Enders, *Chem. Ber.*, 1976, **109**, 1309.

⁵ K. Smith and K. Swaminathan, *J.C.S. Chem. Comm.*, 1975, 719; *J.C.S. Dalton*, 1976, 2297.

with organolithium reagents.^{6,7} In the present study the low yields obtained in some solvents were not caused by the slowness of the deprotonation reaction; use of extended reaction periods caused no improvement. Rather, a competing reaction seems to be responsible. If this is true for the other reactions also, it suggests that the major effect of the solvent is exerted upon the reagent, enhancing its basicity relative to its nucleophilicity. It may be possible, therefore, to generalise these findings to other systems in which organolithium reagents can act as either bases or nucleophiles, and to make suggestions about the solvent systems which would favour either process. For our present purposes, however, we have investigated the synthetic potential of the carbamoyl-lithium (5) prepared under our optimum conditions, by studying its reactions with a variety of electrophiles (Table 2).

TABLE 1

Yields of the glycolamide (6) from di-isopropylcarbamoyl-lithium (5) produced under various conditions

Conditions for production of (5)			Yield of (6) (%) ^a
Solvent(s) (ratio)	Temp. (°C)	Time (min)	
[CH ₂] ₄ O	-78	30	31
Et ₂ O	-78	8	38
(MeO·CH ₂) ₂	-78	30	32
(MeO) ₂ CH ₂	-78	30	50
Et ₂ O-[CH ₂] ₄ O (80 : 20)	-78	30	60
Et ₂ O-[CH ₂] ₄ O-pentane (4 : 4 : 1)	-78	45	76
	-95	45	83

^a For all reactions the ratios of Bu^tLi to HCO·NPr₂ to PhCOPh were 1 : 1 : 1. PhCOPh was added to pre-formed (5) at the temperature of its production, and the mixture was allowed to warm up slowly before work-up. The yield of (6) was estimated by chromatographic isolation.

TABLE 2

Reactions of di-isopropylcarbamoyl-lithium (5) with electrophiles^a

Electrophile	Product ^b	M.p. (°C)	Yield (%) ^c
PhCOPh	Ph ₂ C(OH)·CO·NPr ₂	150	85
PhCHO	PhCH(OH)·CO·NPr ₂	95—95.5	80
MeCOMe	Me ₂ C(OH)·CO·NPr ₂	80—81	81
EtCHO	EtCH(OH)·CO·NPr ₂	(Liq.)	62
[CH ₂] ₅ C:O	[CH ₂] ₅ C(OH)·CO·NPr ₂	141	83
PhCH:CH·CHO	PhCH:CH·CH(OH)·CO·NPr ₂	108—108.5	68
PhCO ₂ Et	PhCO·CO·NPr ₂	124	70
D ₂ O ^d	DCO·NPr ₂	(Liq.)	70 ^e
PhCH ₂ Br	PhCH ₂ ·CHPh·CO·NPr ₂	86.5	68

^a Ratio of HCO·NPr₂ to Bu^tLi to electrophile 1 : 1.1 : ca. 0.8, unless otherwise stated. ^b All isolated products were characterised by their spectral properties and gave satisfactory analyses (see Experimental section or Supplementary Publication). ^c Yield of product after chromatographic purification based upon electrophile, unless otherwise stated. ^d Excess of D₂O used; yield based upon HCO·NPr₂. ^e Estimated by g.l.c. ¹H N.m.r. verified the absence of HCO·NPr₂ in the product.

Representative examples of several types of aldehydes and ketones (aliphatic, aromatic, alicyclic, and αβ-

⁶ B. J. Wakefield, 'Chemistry of Organolithium Compounds,' Pergamon, Oxford, 1974, p. 34; G. Köbrich, *Angew. Chem. Internat. Edn.*, 1967, **6**, 41 (see p. 46).

⁷ G. Köbrich, H. R. Merkle, and H. Trapp, *Tetrahedron Letters*, 1965, 969; see also ref. 3b.

unsaturated) and the only ester tried reacted satisfactorily with (5) to give good yields of the expected products. Reaction with D₂O gave DCONPr₂ with no evidence of residual HCONPr₂. Benzyl bromide also reacted, though the initial product, PhCH₂·CO·NPr₂, was sufficiently acidic for deprotonation and further alkylation to occur.

Less reactive alkylating agents such as iodomethane and 1-iodopropane gave complex mixtures of products suggestive of decomposition of (5) involving little reaction with the electrophile. ¹H N.m.r. spectra indicated the presence of small amounts of the alkylation products, but the reactions were clearly not of synthetic significance, and were not further investigated. A similar result was obtained by Fraser and Hubert^{3c} with the carbamoyl-lithium (5) prepared according to reaction (A). Their rationalisation for the low yields obtained is untenable in our case, and it is perhaps more likely that the low reactivity of iodoalkanes at low temperature, together with the instability of (5) at higher temperatures, is responsible in both cases.

In conclusion, the yields of products from reactions of the carbamoyl-lithium (5) prepared by use of t-butyl-lithium are generally similar to or higher than those from the same reagent prepared by use of lithium di-isopropylamide. Reactions of compound (5) with carbonyl compounds provide useful syntheses of the appropriate α-hydroxy- and α-oxo-amides.

EXPERIMENTAL

Solvents and liquid reagents were purified and dried by standard procedures.⁸ D₂O (Fluorochem) and benzophenone (B.D.H.) were used without further purification. NN-Di-isopropylformamide was prepared from formic acid and di-isopropylamine by the method of Robson and Reinhart.⁹ Solutions of organolithium reagents (Ventron) were estimated by the double titration method.¹⁰ All reactions were carried out under nitrogen (oven-dried apparatus was assembled hot and allowed to cool under reduced pressure, then filled with nitrogen, re-evacuated, and refilled twice more before the start of any experiment). Liquids were transferred by syringe.

Spectra were recorded with Perkin-Elmer 257 (i.r.), Varian HA100 (¹H n.m.r.), and A.E.I. MS9 (mass) spectrometers; for g.l.c. a Perkin-Elmer F11 instrument was used.

Preliminary Investigation of Reactions of NN-Di-isopropylformamide with Organolithium Reagents.—Details of reaction conditions and yields of the product (6) are recorded in Table 1 and in the Supplementary Publication. The apparatus was a 100 ml round-bottomed flask, equipped with stirrer and a septum-capped stop-cock. Di-isopropylformamide (0.33 g, 2.49 mmol) and the appropriate solvent (45 ml) were added, pressure equilibration being achieved by means of a needle pushed through the septum and connected to a paraffin oil bubbler. The flask was placed in a cooling bath set at the appropriate temperature, and the mixture was stirred during the addition of organolithium

⁸ D. D. Perrin, W. L. F. Armarego, and D. R. Perrin, 'Purification of Laboratory Chemicals,' Pergamon, Oxford, 1966.

⁹ J. H. Robson and J. Reinhart, *J. Amer. Chem. Soc.*, 1955, **77**, 498.

¹⁰ H. Gilman and A. H. Haubein, *J. Amer. Chem. Soc.*, 1944, **66**, 1515.

reagent (2.49 mmol*). After the appropriate time benzophenone (0.453 g, 2.49 mmol) in the reaction solvent (9 ml) was added, and the mixture was stirred for 45 min at the reaction temperature before being allowed to warm to ambient temperature. The reaction solvent was removed under reduced pressure and was replaced by dichloromethane (*ca.* 50 ml). The solution was washed with water (2 × 20 ml), dried (MgSO₄), and evaporated under reduced pressure. A qualitative picture of the extent of reaction was obtained by comparison of the intensities of carbonyl i.r. absorptions due to benzophenone at 1670 cm⁻¹ and to the product (5) at 1620 cm⁻¹. A quantitative estimate was obtained by separation on a column of dry silica (*ca.* 50 g). After prior elution with light petroleum, and light petroleum-dichloromethane (50 : 50), the product (6) was eluted with dichloromethane (slowly) or dichloromethane-diethyl ether (80 : 20).

Preparation of NN-Di-isopropyl-2,2-diphenylglycolamide (6).—To di-isopropylformamide (0.31 g, 2.4 mmol) in a flask set up as described above were added tetrahydrofuran (20 ml), diethyl ether (20 ml), and pentane (5 ml), any pressure build-up being released through a needle bubbler. The flask was placed in a crystallising dish filled with acetone, which was cooled by addition of liquid nitrogen until the

* The volume of solvent necessarily added with the reagent is ignored for the figures recorded in the Table. The volume was *ca.* 3 ml, and the solvent generally hexane.

acetone just froze (measured temperature -95 °C). The cooling bath was maintained at a temperature just below the m.p. of acetone, and the mixture was stirred during the addition (over *ca.* 2 min.) of t-butyl-lithium (3.3 ml of 0.8M-solution in hexane, 2.64 mmol), and for 45 min thereafter. Benzophenone (0.33 g, 1.8 mmol) in tetrahydrofuran (4 ml), diethyl ether (4 ml), and pentane (1 ml), was added, stirring was maintained, and with the cooling bath left in place but with no further liquid nitrogen added, the mixture was slowly allowed to warm to ambient temperature (over *ca.* 2 h). It was then worked up and separated as described for the preliminary experiments, to yield the glycolamide (6) (0.47 g, 85% based upon benzophenone), m.p. 150 °C (from benzene-pentane); ν_{CO} 1 620, ν_{OH} 3 215 cm⁻¹; δ (CDCl₃) 7.37 (10 H, m), 6.49 (1 H, s, exchangeable), 3.71 (1 H, septet), 3.33 (1 H, septet), 1.45 (6 H, d), and 0.50 (6 H, d); *m/e* 311 (0.1% of largest peak above *m/e* 50, *M*⁺). 183 [100%, (Ph₂COH)⁺], and 128 [63%, (Pr₂NCO)⁺] (Found: C, 77.5; H, 7.6; N, 4.8. C₂₀H₂₅NO₂ requires C, 77.2; H, 8.0; N, 4.6%).

Preparation of Other α -Hydroxy-amides.—The other reactions referred to in Table 2 were carried out in analogous manner. Full details, including analytical and spectroscopic data for the products, are given in the Supplementary Publication.

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