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N,N-DISUBSTITUTED CARBAMATES, REAGENTS FOR THE PREPARATION OF KETONES.

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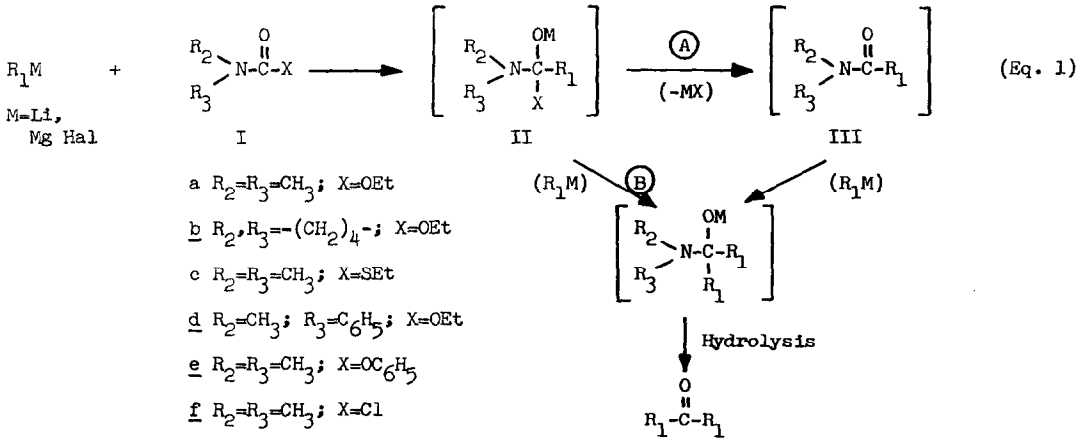
Although organometallic compounds are known to react with carboxamides to yield ketones [1], N,N-disubstituted carbamates (DSC) have not previously been used for their preparation. Thus, interaction of two equivalents of an organometallic compound with one equivalent of DSC (0.5 - 3 hours at -70° to -10° depending on the type of organometallic compound) yields the corresponding symmetrical ketone after hydrolysis. Two possible mechanisms for the reaction are outlined in Eq. 1:



(Eq. 1)

a $R_2=R_3=CH_3$; X=OEt

b $R_2,R_3=-(CH_2)_4-$; X=OEt

c $R_2=R_3=CH_3$; X=SEt

d $R_2=CH_3$; $R_3=C_6H_5$; X=OEt

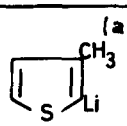
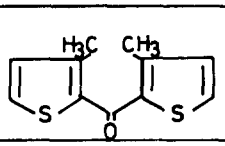
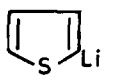
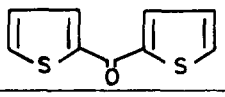
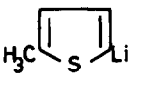
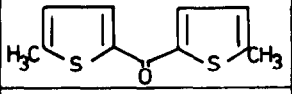
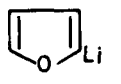
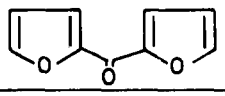
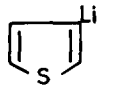
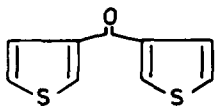
e $R_2=R_3=CH_3$; $X=OC_6H_5$

f $R_2=R_3=CH_3$; X=Cl

The carbamates are easily obtained in high yield (80-94 %) by allowing two equivalents of the corresponding secondary amine (40-50 % in aqueous solution) to react with chloroformic ester, or by the interaction of dimethylcarbamoyl chloride (If) with a suitable carbinol. The advantages of the present method are its simplicity, short reaction time and ease of handling of the reagents, with the possibility of working on large scales.

Typical results are collected in Table 1. Special attention was paid to the preparation of heterocyclic ketones, since these compounds are usually prepared by multi-step syntheses. Many satisfactory methods are available for the preparation of aliphatic and aryl ketones.

Table 1. Symmetrical ketones obtained according to Eq. 1

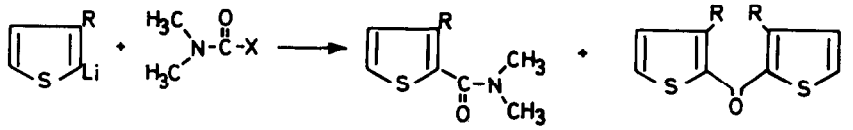
Organometallic compound	DSC	Product (b)	Yield ; b.p.; (m.p.)	
			This work	Literature
 (a)	Ia		[3] 75%; 125°-126°/0.4	———
	Ia If		92%; (87°-89°) 90%;	[4] 66%; (88°-89°)
	Ia		60%; 125°-126°/0.01 (50°-51°)	[5] 88%; 212°-214°/13 (48°-49°)
	Ia	 (c)	71%; 90°-92°/0.01	[6] 27%; 110°/0.05
	Ia Ie If		45%; 190°-195°/12 57%; (75°-76°) 89%;	[7] 71%; (78°-80°)
$n\text{-}C_4H_9MgBr$	Ia	$(n\text{-}C_4H_9)_2CO$	53%; 187°	188°

(a) Prepared by interaction of 10 % excess of ethereal ethyllithium with 3-methyl-2-bromothiophene [2] at -70° for 15 min. (b) Hydrolysed with cold 3 N HCl. (c) Hydrolysed with cold saturated ammonium chloride solution.

When carbamates Ia-e were allowed to react with the same organometallic compound under similar conditions, whilst carbamates Ia,b,c,e gave practically the same yield of product, N-methyl-N-phenylurethane (Id) gave only traces of the expected ketone.

It was of mechanistic and preparative interest to investigate the validity of the mechanisms proposed in Eq. 1. If the interaction of the second equivalent of organometallic reagent with the intermediate compound II (path B), or with the disubstituted amide III (path A) were rate

determining, it would be possible to prepare unsymmetrical ketones by use of two different organometallic reagents. In the preliminary investigation 3-methyl-2-thienyllithium (0.05 mole) was allowed to react with equivalent amounts of carbamates (Ia,c,e,f, Eq. 2) for 30 minutes at -70° and 2-thienyllithium was allowed to react with an equivalent amount of dimethylcarbamoyl chloride at various temperatures for 30 minutes. The reaction mixtures were hydrolysed and analysed by g.l.c. Authentic samples of N,N-dimethyl-3-methyl-2-thienylcarboxamide (IIIA) and N,N-dimethyl-2-thienylcarboxamide (IIIB) were prepared by allowing the corresponding acid chlorides to react with aqueous dimethylamine [8].



(Eq. 2)

I III IV

A R=CH_3

B R=H

The amide (IIIA)/ketone (IVA) distributions obtained using g.l.c. analysis are listed in Table 2.

Table 2. Amide (IIIA)/ketone (IVA) distributions determined by g.l.c.

X	% Amide (IIIA)	% Ketone (IVA)
OEt	10.5	89.5
SEt	7.5	92.5
OC_6H_5	55	45
Cl	>98	2 >

From these results it is difficult to distinguish between path A and B in Eq. 1, as it is possible that the amide being detected is an artifact produced from the proposed "hemiketal" (II) during hydrolysis. Except for DSC Ic, the results are in agreement with the known "departing abilities" [9] that these substituents show during nucleophilic substitution reactions. For dimethylcarbamoyl chloride, the last step, whether it is a substitution or an addition, is rate determining, thus allowing the preparation of unsymmetrical ketones. The reaction between 2-thienyllithium and dimethylcarbamoyl chloride was investigated at -40°, -70° and -95°. The percentages of amide IIIB in the reaction mixtures were 22, 67 and 25 respectively. Again, at -70° the amide (IIIB) is the major product, but not in high enough yield to allow the efficient synthesis

of unsymmetrical ketones. The difference in the relative amounts of the amides produced from the two organolithium compounds might be due to steric effects present in the intermediate IIA (derived from 3-methyl-2-thienyllithium, Eq. 1). At -70°, under similar conditions, reaction between N,N-dimethyl-2-thienylcarboxamide (IIIB) and 2-thienyllithium gave 50 % of di-(2-thienyl)ketone, which does not indicate whether the "free" amide (IIIA) is an intermediate in the reaction.

A mechanistic investigation of the above reaction for the preparation of unsymmetrical ketones is being undertaken. The scope of this reaction for the preparation of cyclic ketones is also being examined.

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[3] Analysed for $C_{11}H_{10}OS_2$: C 59.4; H 4.53; S 28.8. Found: C 59.6; H 4.70; S 28.5.

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[7] S. Gronowitz and B. Eriksson, Arkiv Kemi 21, 335 (1964).

[8] N,N-Dimethyl-3-methyl-2-thienylcarboxamide, b.p. 75-77°/0.002 was prepared in 67 % yield from 3-methyl-2-bromothiophene. Analysed for $C_8H_{11}NOS$: C 56.8; H 6.55; N 8.28; S 18.95. Found: C 56.5; H 6.67; N 8.21; S 18.8. N,N-Dimethyl-2-thienylcarboxamide, b.p. 145-148°/12-13, prepared in 52 % yield from 2-thiophenecarboxylic acid. Analysed for C_7H_9NOS: C 54.17; H 5.85; N 9.02; S 20.65. Found: C 53.73; H 6.01; N 9.09; S 21.10.

[9] E.S. Gould, "Mechanism and Structure in Organic Chemistry", pp. 258-263, Holt, Rinehart and Winston, New York, 1959.