Tetrahedron Vol. 35, pp. 2077 to 2079
Pergamon Press Ltd., 1979. Printed in Great Britain

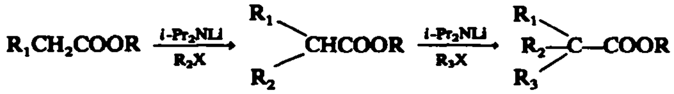
STERIC HINDRANCE IN SYNTHESIS
DEALKYLATION OF HINDERED CARBOXYLIC ESTERS *via* THE ACTION OF ORGANOLITHIUM REAGENTS. SYNTHETIC AND MECHANISTIC ASPECTS

CLAUDE LION, JACQUES-EMILE DUBOIS,* J. ANTHONY MACPHEE and YAYÉ BONZOUGOU
Institut de Topologie et de Dynamique des Systèmes de l'Université Paris VII, Associé au C.N.R.S., 1, rue Guy de la Brosse, 75005 Paris, France

(*Received in UK 5 March* 1979)

Abstract—The reaction of n-propyllithium with a number of hindered aliphatic carboxylic esters in ether at 0° produces cleanly the corresponding carboxylic acid in satisfactory yields. This reaction represents a facile dealkylation of hindered carboxylic esters. The mechanistic aspects are briefly examined.

Interest in highly hindered molecules, both at the theoretical and the synthetic level, has grown widely in the past few years.[1] In the case of carboxylic esters the current state of the art allows the synthesis of the hindered structures: i-Pr$_3$CCOOR[2] and t-Bu$_2$CHCOOR.[3,4] Recent work carried out in this laboratory now permits facile access to a large number of hindered esters.[5,6] Modification and optimization of alkylation techniques described by Schlessinger[7] makes this possible via the following reaction sequence:



$$R_1CH_2COOR \xrightarrow[R_2X]{i\text{-}Pr_2NLi} \begin{matrix} R_1 \\ \quad \rangle CHCOOR \\ R_2 \end{matrix} \xrightarrow[R_3X]{i\text{-}Pr_2NLi} \begin{matrix} R_1 \\ R_2\text{—}C\text{—}COOR \\ R_3 \end{matrix}$$

The structures thereby obtained (Table 1) are isomeric to i-Pr$_3$CCOOR (t-Bui-PrEtCCOOR) and t-Bu$_2$CHCOOR (t-Bui-PrMeCCOOR, t-BuEt$_2$CCOOR and i-Pr$_2$EtCCOOR).

As a part of our continuing studies on highly hindered compounds we investigated the reaction between organolithium reagents and these highly hindered esters. This reaction has most often been studied in the case of linear esters and yields at low temperature the corresponding ketone along with the tertiary alcohol.[8,9] Various workers have investigated the effect of the chain branching in the organolithium reagent, chain lengthening of the esters, relative proportions of reagents and temperature:[8-10]

$$RCOOEt + R'Li \longrightarrow R\text{—}CO\text{—}R' + RC(OH)R'_2$$

In the case of more substituted esters and a tertiary organolithium the condensation leads cleanly to the ketone: thus hexamethylacetone t-BuCOt-Bu has been obtained by the condensation of t-BuLi on ethyl pivalate, t-BuCOOEt in 83% yield.[10] In the case or aromatic esters the condensation gives mainly tertiary alcohols.[11]

The reaction of n-propyllithium on a number of hindered carboxylic esters follows however a totally different course: *it is in fact an excellent method of dealkylation of hindered carboxylic esters*, i.e. the facile preparation of the corresponding carboxylic acids.[12]

Over the past few years the various methods of saponification or dealkylation of esters have been studied in some detail. In addition to the traditional method using strong bases in differing solvents,[13] numerous recent methods are available: the reaction of lithium in liquid ammonia,[14] Lewis acids such as BCl$_3$[15] and those reagents capable of effectuating C–O scission. Among the latter are organic bases,[16] diaza-1,5 bicyclo (4.3.0)-5-nonene,[17] thioethoxide and n-propoxide anions in DMF[18,19] or HMPA,[20] potassium t-butoxide in DMSO,[21] potassium hydride,[22] potassium superoxide[23] and chlorotrimethylsilane in the presence of sodium iodide.[24] The present work shows that organolithium reagents belong in this category and are capable of breaking carbon–oxygen bonds in hindered esters.

Technically facile our method involves the reaction of esters (Table 1) with an excess of n-propyllithium in ether at 0° for 36 hours. The yields

Table 1. Condensation of n-propyllithium with hindered esters in ether at 0° for 36 hours

n°	ester	acid (yield %)
1	t-Bui-PrEtCCOOEt	61
2	t-BuEt$_2$CCOOEt	44
3	t-Bui-PrMeCCOOEt	77
4	t-Bui-PrMeCCOOMe	39
5	t-Bui-PrMeCCOOtBu	82
6	t-Bui-PrMeCCOOnC$_8$H$_{17}$	72
7	i-Pr$_3$CCOOEt	53
8	i-Pr$_2$EtCCOOEt	42
9	i-Pr$_2$MeCCOOEt	72

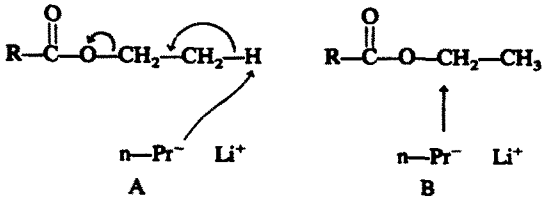
Table 2. Synthesis of the esters $R_1R_2CHCOOEt$ and $R_1R_2R_3CCOOEt$

n°	R_1	R_2	R_3	bp°/mm Hg	yield (%)	litt.[5]
–	i-Pr	Me	H	51–53°/48 mm	97	95
–	i-Pr	Et	H	51–55°/18 mm	98	95
–	t-Bu	Me	H	61–63°/25 mm	92	99
–	t-Bu	Et	H	82–88°/60 mm	96	96
1	t-Bu	Et	iPr	98–103°/10 mm	60	60
2	t-Bu	Et	Et	108–110°/15 mm	78	78
3	t-Bu	Me	i-Pr	91–92°/12 mm	96	94
7	i-Pr	i-Pr	i-Pr	98–101°/15 mm	42	42
8	i-Pr	Et	i-Pr	83–87°/15 mm	81	81
9	i-Pr	Me	i-Pr	100–102°/38 mm	76	99

are variable and in general satisfactory. The reaction is clean since only acid and ester are recovered. This is an important feature when precious compounds are to be dealkylated.

In general organolithium reagents lead (by a 1–2 addition process), to ketonic and alcoholic products. In the present case the formation of carboxylic acids in good yields is surely attributable to the steric hindrance. Recent work on steric effects by us shows that all the groups present in the table (the acyl moiety) are greater than 6 powers of ten more hindered than methyl (e.g. E_s' (i-Pr_3C–) = −6.73).[25] This high degree of steric hindrance at the carbonyl group is sufficient to inhibit attack on the carbonyl group and allows another reaction to take place. It is interesting to note that in case of the aromatic ester ethyl 2,4,6 triisopropylbenzoate, dealkylation has not been reported but rather α-lithiation.[26] Presumably stabilization of carbanionic species is possible in the case of an aryl but not an alkyl moiety.

The results in the table may be rationalized in terms of two mechanistic pathways. Path A involves β-elimination resulting in the formation of the lithium salt of the acid, ethylene and propane; path B occurs by nucleophilic attack on the α-carbon resulting in the lithium salt of the acid and pentane.[27]



Products studies show that Path B seems to be favoured in the case of dealkylation by t-BuO^-K^+ in DMSO as well as n-PrS^- in DMF or HMPA.

In order to gain information on the mechanism of this reaction experiments **3**, **4**, **5**, **6** were carried out varying the alkoxy moiety of the ester while maintaining the acyl moiety fixed. In the case of methyl ester **4**, the yield is distinctly lower (39%) than for the ethyl ester **3** 77%. The fact that dealkylation occurs at all in the case of **4** indicates that the path B is operating. The increased yield of acid for the ethyl ester **3** (77%) as well as the t-butyl ester **5** (82%) shows that path A is important as well in these cases. The isolation of 1-octene as a reaction product of the n-octyl ester **6** establishes unambiguously the existence of path A. It is therefore apparent that there is a mechanistic dichotomy and that the proportion of reaction via path A or B in a given case depends upon the structural features of reactants.

Overview. The regioselectivity of the reaction of an ester with a base or nucleophile may be effectively controlled using the tool of increasing steric hindrance. Thus, for example, the formation of ester enolates is favoured in the case of triethylcarbinyl esters in liquid ammonia since the large steric effect of the group Et_3C– prevents attack on the carbonyl.[2] Enolization is likewise favoured in the case of relatively simple aliphatic esters by using the hindered base, i-Pr_2NLi. When the acyl portion of the ester is hindered, enolization as well as nucleophilic attack are disfavoured in this part of the molecule.[5–7] In this case either deprotonation or dealkylation may take place: ethyl 2,4,6-triisopropylbenzoate reacts with s-butyllithium to give the α-lithiated species while hindered aliphatic carboxylic esters tend to undergo dealkylation. The reaction of n-propyllithium on hindered carboxylic esters has been shown in this paper to be an example of this latter category providing a facile method for dealkylating hindered carboxylic esters in satisfactory yields.

EXPERIMENTAL

All the products were identified by their IR (Perkin Elmer 225) and NMR (Jeol C60 HL) spectra.

The α,α-disubstituted and α,α,α-trisubstituted esters $R_1R_2CHCOOEt$ and $R_1R_2R_3CCOOEt$ have been described in our previous work.[5,6] In Table 2 we give only, the boiling points and the yields obtained in the synthesis of these compounds.

Table 3. Acids obtained in the dealkylation of the esters, $R_1R_2R_3CCOOH$

R_1	R_2	R_3	m.p.	litt.
t-Bu	Et	i-Pr	90°	89–90°[6]
t-Bu	Me	i-Pr	61°	58–61°[6]
t-Bu	Et	Et	98°	98–99°[6]
i-Pr	i-Pr	i-Pr	149°	148–149°[2]
i-Pr	Et	i-Pr	48–49°	48–49°[6]
i-Pr	Me	i-Pr	liq.	liq.[6]

The esters **4**, **5** and **6** have been obtained by the reaction of the acid chloride t-Bui-PrMeCCOCl[6] with the corresponding commercial alcohol.

General dealkylation procedure. To a sol of 10 mmoles of the ester in 10 ml of dry ether cooled at 0°, 2 M n-PrLi in ether (4 equivs) was added. The temp was kept at 0° for 36 h with magnetic stirring under an inert atmosphere, then poured onto ice. The ethereal sol dried over $MgSO_4$ gave unreacted material. The aqueous layer was acidified by 10% HCl and extracted to give after drying over $MgSO_4$ the corresponding acid (the yields are given in Table 1).

REFERENCES

[1] T. T. Tidwell, *Tetrahedron* **34**, 1855 and ref. therein (1978).

[2] M. S. Newman and T. Fukunaga, *J. Am. Chem. Soc.* **85**, 1176 (1963).

[3] M. S. Newman, A. Arkell and T. Fukunaga, *Ibid.* **82**, 2498 (1960).

[4] J. Abruscato and T. T. Tidwell, *J. Org. Chem.* **37**, 4151 (1972).

[5] J. A. MacPhee and J. E. Dubois, *J. Chem. Soc.* Perkin I, 694 (1977).

[6] C. Lion, J. E. Dubois and Y. Bonzougou, *J. Chem. Research* M46 S826 (1978).

[7] R. J. Cregge, J. L. Hermann, C. S. Lee, J. E. Richman and R. H. Schlessinger, *Tetrahedron Letters* 2425 (1973); J. L. Hermann and R. H. Schlessinger, *Ibid.* 2429 (1973).

[8] A. D. Petrov, E. Sokolova and G. Chin Lan, *Bull. Soc. Chim. Fr.* 178 (1958).

[9] A. D. Petrov, E. P. Kaplan and Y. Cir, *Ibid.* 1593 (1961).

[10] J. E. Dubois, B. Leheup, S. Molnarfi, F. Hennequin and P. Bauer, *Ibid.* 2024 (1964).

[11] F. Huet and G. Emptoz, *J. Organometallic Chem.* **101**, 139 (1975).

[12] The reaction of t-BuLi on t-Bu_2CHCOOR has been reported by Tidwell (ref 4). With hindered aromatic esters see P. Kaplan, S. V. Zakharova and A. D. Petrov, *Zh. Obsch. Khim.* **33**, 2103 (1963) and A. D. Petrov, E. P. Kaplan and M. Kurash, *Ibid.* **32**, 19 (1962). Generally a mixture of starting material addition and dealkylation products are obtained in various yields.

[13] A. I. Vogel, Practical Organic Chemistry Lowe et Brydone London, 1063 (1970).

[14] E. Wenkert et B. G. Jackson, *J. Am. Chem. Soc.* **80**, 217 (1958).

[15] P. S. Marchang, *J. Chem. Soc.* (D), 667 (1971).

[16] J. E. McMurry et G. B. Wong, *Syn. Comm.* **2**, 389 (1972).

[17] D. H. Miles et E. J. Parrish, *Tetrahedron Letters* 3987 (1972).

[18] G. I. Feutrill et R. N. Mirrington, *Ibid.* 1327 (1970).

[19] W. R. Vaughan et J. B. Baumann, *J. Org. Chem.* **27**, 739 (1962).

[20] P. A. Bartlett et W. S. Johnson, *Tetrahedron Letters* 4459 (1970).

[21] F. C. Wood et N. F. Chang, *Ibid.* 2969 (1969).

[22] J. W. Huffman et P. G. Harris, *Chem. Comm.* 481 (1976).

[23] J. San Filippo, L. J. Romano, Ch. I. Chern et J. S. Valentine, *J. Org. Chem.* **41**, 586 (1976).

[24] T. Morita, Y. Okamoto and H. Sakurai, *J. Chem. Soc.* Chem. Comm. 874 (1978).

[25] J. A. MacPhee, A. Panaye and J. E. Dubois, *Tetrahedron Letters* 3293 (1978); and *Tetrahedron* **34**, 3553 (1978).

[26] P. Beak and B. G. MacKinnie, *J. Am. Chem. Soc.* **99**, 5213 (1977); P. Beak, M. Baillargeon and L. G. Carter, *J. Org. Chem.* **43**, 4254 (1978).

[27] For a general review of the cleavage reaction of ethers by alkyllithium see G. E. Coates and K. Wade, *Organometallic Compounds* Vol. 13, Chap. 1. Methuen, London (1967).