ELSEVIER

Journal of Fluorine Chemistry 86 (1997) 185–187

JOURNAL OF FLUORINE CHEMISTRY

Trifluoromethylketones chemistry: efficient access to silyl enol ethers or silyl carbinols using lithium diisopropylamide

Olivier Provot, Jean-François Berrien, Henri Moskowitz, Joëlle Mayrargue *

Laboratoire de Chimie Organique, associé au CNRS, Université de Paris-Sud, Faculté de Pharmacie, F 92296 Châtenay-Malabry, France

Received 12 May 1997; accepted 30 June 1997

Abstract

Lithium diisopropylamide, reacts with trifluoromethylketones either as a base in polar solvents or as a hydride donor in hexane. In the presence of *tert*-Butyldimethylsilyl chloride, Lithium diisopropylamide allows the transformation of trifluoromethylketones into silyl enol ethers or silyl carbinols using an appropriate solvent. © 1997 Elsevier Science S.A.

Keywords: Lithium diisopropylamide; Trifluoromethylketones; Reduction; Silyl enol ethers

During the last decades, numerous methodologies have been developed in order to prepare fluorine-containing compounds. These applications stem from the fact that the introduction of fluorine into aliphatic molecules has a profound effect upon the physical and chemical properties and modifies the physiological activity of resulting compounds [1–4].

In connection with the synthesis of various fluorinated terpenes, we had to develop a method of protection of the trifluoromethylketone function against a nucleophile such as a Wittig reagent (PPh_3CHOMe). The cleavage of this protective group had to be performed in neutral or basic conditions to preserve the acid sensitive enol ether. While several methods have been used hitherto for the synthesis of trifluoromethylketones [5], efficient procedures to block temporarily the trifluoromethyl carbonyl group have not previously been reported.

We first prepared cyclic thioketals [6] but cleavage did not occur, all methods we used were found to be ineffective to regenerate the parent ketone. We think that the high electronegativity of the trifluoromethyl group did not allow oxidation of the sulphur atoms [7].

So we envisaged to protect trifluoromethylketones as their corresponding silyl enol ethers. Silyl enol ethers can be prepared by the condensation of phosphonium ylides with trimethylsilyl trifluoroacetate [8] or from trifluoromethylketones [9], using the methodology described by House et al. [10]. This latter reaction has never been further developed.

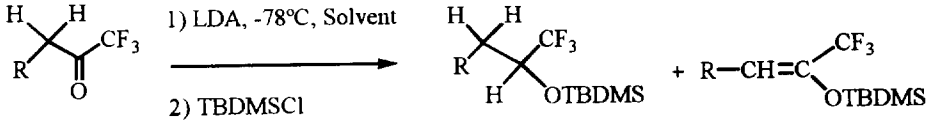
We tested this procedure on various trifluoromethylketones using lithium diisopropylamide (LDA) and *tert*-butyldimethylsilyl chloride (TBDMSCl) at low temperatures (−78°C). The reaction sequence is shown in Scheme 1; products, experimental conditions and yields are listed in Table 1.

In polar solvents (HMPA/THF), the trifluoromethylketo group was converted into silyl enol ether (**b**) in good yields (entries 1,2,3,4,5,7). Cleavage of these silyl compounds, as in the case of non-fluorinated ketones, could be accomplished quantitatively with tetrabutylammonium fluoride in CH_3CN.

In THF, competitive reactions led to a mixture of silyl enol ethers (**b**) and silyl carbinols (**a**) which could not be easily separated.

More surprising results were observed in a less polar solvent. In hexane, using LDA, trifluoromethylketones selec-

* Corresponding author.

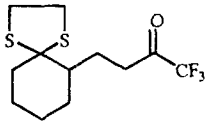
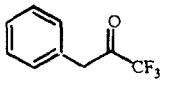
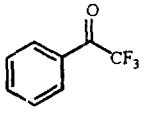
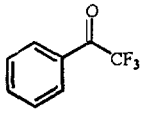


a **b**

Scheme 1.

PII S0022-1139(97)00098-5

Table 1

	Trifluoromethylketone [a]	Base	in THF/HMPA:2/1 (**a/b**)	Y% [b]	in THF[c] (**a/b**)	Y%	in Hexane (**a/b**)	Y%
1	CH_3–$(CH_2)_6$–$COCF_3$	LDA 1eq	0/100	74	50/50	77	100/0	71
2		LDA 1eq	0/100	90	59/41	81	100/0[d]	81
3	CH_3–$(CH_2)_6$–CH=CH–$(CH_2)_6$–$COCF_3$	LDA 1eq	0/100	83	74/26	91	100/0	90
4	CH_3–$(CH_2)_{14}$–$COCF_3$	LDA 1eq	0/100	80	55/45	75	100/0	71
5	CH_3–$(CH_2)_{14}$–$COCF_3$	LiHMDS 1eq	0/100	63	–	–	Starting ketone unchanged	0
6	CF_3–CO–CH_3	LDA 1eq	Degradation	0	–	–	Degradation	0
7		LDA 1eq	0/100	60	54/46	51	100/0	67
8		LDA 1eq	100/0	20	–	–	100/0 No silylation	40
9		LDA 2eq	100/0	30	–	–	100/0 No silylation	60

[a] According to the procedure described by Zard [11] and Burger [12].
[b] The reaction led to a single isomer, the configuration of which could not be determined.
[c] In THF ratio a/b was established by ^1H and ^{19}F NMR spectroscopy.
[d] Mixture 1/1 of diastereoisomeric silyl carbinols.

tively underwent a reduction to alcohols followed by silylation in good yields (entries 1,2,3,4,7). When the same reaction was carried out without TBDMSCl, the free alcohols were obtained as after a classical reduction e.g. $NaBH_4$.

In the particular case of 1,1,1-trifluoroacetophenone (deactivated carbonyl and no *alpha* hydrogen), the reduction occurred in low yields with one or two equivalents of LDA (20% to 30%) in a polar solvent, but yields were slightly increased in hexane (40% to 60%; entry 8,9). In this case, the silylation of stabilised alcoholate did not occur and free alcohols were obtained.

When the reaction was carried out with lithium hexamethyldisilazide (LiHMDS), instead of LDA, no reduction was observed in hexane (entry 5).

In order to establish that this unusual behaviour was specific to trifluoromethylketones, we verified that non-fluorinated ketones such as 2-decanone did not react with LDA in hexane. Moreover, the presence of *alpha* hydrogen on the amide was necessary to perform the reduction (entry 5).

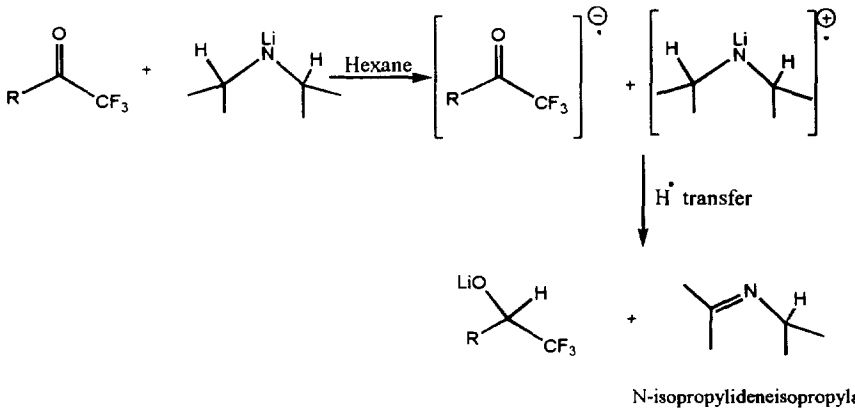
Trifluoromethylketones are known to be easily reduced [13,14] in the presence of Grignard reagents. In an early report, Kowalski et al. [15] observed that LDA reacted with α-halo and α-methoxyketones in Et_2O or THF, to give generally a mixture of reduction products in competition with enolization. To our knowledge, the literature does not mention the reduction of trifluoromethylketones with lithium dialkylamides.

In order to explain the mechanism of the reduction and definitively prove that LDA reacted as a hydride donor in hexane and was oxidised during the reaction, we treated the crude mixture with aqueous HCl. Analysis of the aqueous layer by ^{13}C NMR spectroscopy in D_2O showed two products which were identified as diisopropylamine hydrochloride (which came from slight excess of diisopropylamine) and monoisopropylamine hydrochloride which was formed after acidic hydrolysis of *N*-isopropylideneisopropylamine [16].

To explain the reducing action of LDA, Kowalski et al. [15] and Benkeser and De Boer [17] suggested an ionic mechanism via a six membered ring. In hexane, as proposed by Felix et al. [14], we suppose a single electron transfer (Scheme 2) via a stable ketyl radical anion intermediate to explain this total and unprecedented reduction.

It has been found that the solvent has a determining effect at −78°C on the reaction between LDA and trifluoromethylketones. In a polar solvent such as THF-HMPA, trifluoromethylketones were transformed into their silyl enol ethers whereas in hexane they were reduced and isolated as silyl carbinols in a one step synthesis.

When a mixture of 1,1,1-trifluoro-2-heptadecanone and 2-decanone (or cyclohexanone) was treated with LDA in hex-



Scheme 2.

ane at −78°C, the trifluoromethylketone was totally reduced whilst the hydrocarbon ketones remained unchanged. In this case, best yields of this chemoselective reduction are obtained by adding first 1.1 eq of TBDMSCl and then LDA in order to prevent nucleophilic attacks of fluorinated alcoholates on the hydrocarbon ketones.

Acknowledgements

The authors are indebted to Dr. Ourévitch for ^{19}F N.M.R. work and to Dr. Bégué and Bonnet-Delpon for helpful discussions. Financial support from the DRED (réseau de Recherche 'Pharmacochimie') was greatly appreciated.

References

[1] W.A. Sheppard, C.M. Sharts, Organic Fluorine Chemistry, Benjamin, New York, 1969.
[2] J.T. Welch, S. Eswarakrishnan, Fluorine in Bioorganic Chemistry, Wiley, New York, 1991.
[3] J.T. Welch (Ed.), Selective Fluorination in Organic and Bioorganic chemistry, Am. Chem. Soc., Washington, DC, 1991.
[4] Abeles, R.H., Alston, T.A., J. Biol. Chem. 265 (1990) 16705.
[5] Bégué, J.P., Bonnet-Delpon, D., Tetrahedron, 47 (1991) 3207.
[6] Kuroboshi, M., Hiyama, T., J. Fluorine Chem. 69 (1994) 127.
[7] Aubert, C., Bégué, J.P., Charpentier-Langlois, M., Née, G., Langlois, B., J. Fluorine Chem. 44 (1989) 377.
[8] Bégué, J.P., Mesureur, D., J. Fluorine Chem. 39 (1988) 271.
[9] Liang, T., Abeles, R.H., Biochemistry, 26 (1987) 7603.
[10] House, H.O., Czuba, L.J., Gall, M., Olmstead, H.D., J. Org. Chem. 4 (1969) 2324.
[11] Boivin, J., El Kaim, L., Zard, S.Z., Tetrahedron, 51 (1995) 2573.
[12] Nes, W.R., Burger, A., J. Am. Chem. Soc. 72 (1950) 5409.
[13] McBee, E.T., Pierce, O.R., Higgins, J.F., J. Am. Chem. Soc. 74 (1952) 1736.
[14] Felix, C., Laurent, A., Mison, P., J. Fluorine Chem. 70 (1995) 71.
[15] Kowalski, C., Creary, X., Rollin, A.J., Carmel Burke, M., J. Org. Chem. 43 (1978) 2601.
[16] Norton, D.G., Haury, V.E., Davis, F.C., Mitchell, L.J., Ballard, S.A., J. Org. Chem. 19 (1954) 1054.
[17] Benkeser, R.A., De Boer, C.E., J. Org. Chem. 21 (1956) 281.