Pergamon

Tetrahedron Letters, Vol. 37, No. 2, pp. 171-174, 1996

0040-4039/96 $15.00 + 0.00

0040-4039(95)02118-3

Z-Trifluoromethyl Thioenol Ethers, Enol Ethers, and Enamines; Reactivity Towards Organolithium Reagents.

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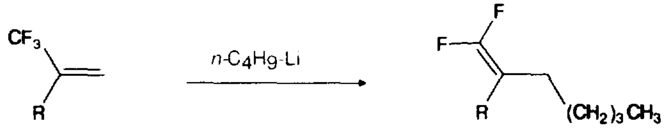
Keywords- *Trifluoromethyl -alkenes, -dienes, -enol ethers, -thio enol ethers, -enamines, organolithium reagents, addition/elimination*

Abstract: Trifluoromethyl enol ethers and thioenol ethers conjugated with an unsaturation in the β-position undergo addition/elimination reactions with organolithium reagents to yield the corresponding trifluoromethyl alkenes while preserving the geometry of the double bond. Trifluoromethyl enamines exhibit a different reactivity towards organolithium reagents with a vinyl anion being formed in preference to addition/elimination products.

It has been reported that *n*-butyllithium readily reacts with the trifluoromethyl thioenol ether **1a**[1] and alkenes **1b-c**,[2,3] to give the corresponding *gem*-difluoroalkenes in good yields (Scheme 1). This reaction has been extended to more synthetically useful organolithium reagents in the case of 1,1,1-trifluoropropene **1b**[4,5] and α-trifluoromethyl styrene **1c**,[3,6] to give access to a wide range of functionalised *gem*-difluoroalkenes.



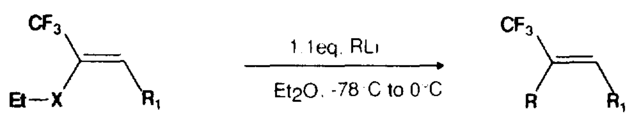
1a R= PhS, **1b** R=H, **1c** R= Ph **2a-c** 60-93%

Scheme 1

However despite this high reactivity of α,α-disubstituted alkenes of type **1** with organolithium reagents, little has been reported on the reactivity of other types of trifluoromethyl alkenes. In this note, we wish to report our investigations into the reactivity of α,β-disubstituted trifluoromethyl alkenes, in particular the Z-trifluoromethyl thioenol ethers **3**,[7] enol ethers **4**[8] and enamines **7**[9], towards organolithium reagents.

The trifluoromethyl thioenol ether **3a** was found to be unreactive towards *n*-butyllithium, the thioenol ether being recovered even after prolonged reaction times at 0°C. However the thioenol ether **3b** bearing a phenyl substituent in the β-position easily reacted with *n*-butyllithium, not resulting in the formation of a *gem*-difluoro alkene as reported for **1a**[1] but in the formation of the trifluoromethyl alkene **5b**, in which the ethylthio group was replaced by a *t*-butyl group.[10] The geometry of the double bond in the starting alkene was conserved, as demonstrated by NOE experiments: irradiation of the *t*-butyl group resulted in an enhancement of an *ortho* aromatic proton, indicating a spatial proximity of the *t*-butyl and phenyl groups.

The high selectivity of this reaction prompted us to investigate the reactivity of other commercial organolithium reagents towards **3b**. In all cases, the only products detected were the trifluoromethyl alkenes **5b** which were formed in good yields with complete conservation of the geometry of the double bond. The same reactivity was observed for the trifluoromethyl enol ether **4b**, with the ethoxide group selectively replaced to give the alkenes **5b**. This reaction is also applicable to other conjugated systems: for example dienes **3c** and **4c** reacted in a similar way (table 1).



3 X= S **a:** R1= (CH2)2Ph, **b:** R1= Ph, **c:** R1= CH=CHPh **5**
4 X= O **a:** R1= (CH2)2Ph, **b:** R1= Ph, **c:** R1= CH=CHPh

R_1	RLi	Yield%[a] X=S	X=O
$(CH_2)_2Ph$	n-C_4H_9Li	0	0
Ph	t-C_4H_9Li	90	84
Ph	n-C_4H_9Li	85	79
Ph	CH_3Li	87	82
Ph	PhLi	83	85
CH=CHPh	t-C_4H_9Li	70	75
CH=CHPh	CH_3Li	80	77

[a] yields refer to chromatographically pure compounds[11]

Table 1

The formation of the alkenes **5** can be envisaged through the *cis* addition of the organolithium reagent to the double bond of the trifluoromethyl thioenol ethers **3b-c** or enol ethers **4b-c** to form an intermediate in which the lithium atom is adjacent to the R_1 group, followed by a *trans* elimination of lithium ethoxide/ lithium ethyl thiolate to give **5**. This reaction is formally a substitution of an ethoxy or ethylthio group by an alkyl group. Such *pseudo* substitutions are well documented for the reaction of organolithium reagents with *gem*-difluoroalkenes[12] and perfluoroalkyl alkenes,[13,14] in which a fluorine atom is the leaving group. The displacement of the ethoxy or ethylthio group instead a fluorine atom is determined by the orientation of the initial addition of the organolithium reagent to the double bond.

All attempts to form **6** by trapping the postulated intermediate in the reaction of an organolithium reagent with **4b** for example, by performing the reaction in the presence of trimethylsilyl chloride/TMEDA, failed, suggesting that the elimination of lithium ethoxide is instantaneous. This result prompted us to investigate the addition of organolithium reagents to the trifluoromethyl enamine **7**: the amine function being a poor leaving group, the degree of stability of the intermediate should be increased. All attempts to exchange the amine function for an alkyl substituent, by treatment with an organolithium reagent, resulted in the recovery of starting **7** after aqueous work up. However surprisingly, treatment of **7** with 1.1 equivalent of *n*-butyllithium at -10°C for one hour, followed by the addition of trimethylsilyl chloride, resulted in the formation of the vinyl silane **8** in a 40% conversion, indicating the formation of a vinyl anion. This result suggests that a good leaving group is one of the prerequisites for the addition of organolithium reagents to trifluoromethyl alkenes.

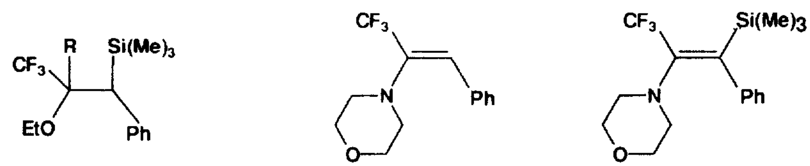


Figure 1

In summary, we have demonstrated that the addition of organolithium reagents to *Z*-trifluoromethyl -thioenol ethers and enol ethers conjugated with an unsaturation in the β-position, results in the formation of the corresponding trifluoromethyl alkenes and dienes with conservation of geometry of the double bond. This procedure offers an alternative route to the Wittig reaction between a trifluoromethyl ketone and an ylide, with the opposite stereoisomer being formed to that normally obtained.[15] In addition, this procedure allows an access to sterically hindered trifluoromethyl alkenes which cannot be prepared by the Wittig reaction due the difficulties in preparing sterically hindered trifluoromethyl ketones.[16]

Acknowledgements: This work was supported by CNRS and European Community Network on Synthesis and Molecular Recognition of Selectively Fluorinated Bioactive Molecules (ERBCHRXCT930279). We thank Michèle Ourevitch for her invaluable high-field NMR experiments.

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(10) Typical procedure: To a solution of the thioenol ether **3b** (0.5 g, 2.15 mmol) in diethyl ether (25 mL) at -78°C was added *t*-Buli (1.45 mL of a 1.6 M solution in hexanes). The solution was stirred for a further 15min at -78°C, and then allowed to warm to 0°C over 1h. The resultant brown reaction mixture was then poured into saturated ammonium chloride solution (25 mL) and extracted with diethyl ether (3 x 70 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give a brown oil which was purified by chromatography on silica gel (eluent: pentane-Et_2O: 95:5) to give the pure *E*-2-trifluoromethyl-2-*t*-butyl styrene **5b** (0.44g, 90%). I.R neat 1645 cm^{-1} (νC=C); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ -60.3; ^{1}H NMR ($CDCl_3$) δ 1.1 (s, 9H), 7.1-7.4 (m, 6H (=C$\underline{H}$ + $C_6\underline{H}_5$); ^{13}C NMR ($CDCl_3$) δ 31.2 ($\underline{C}H_3$), 34.9 ($\underline{C}(CH_3)_3$), 125.1 (q, $^{1}J_{CF}$ = 277.5 Hz, $\underline{C}F_3$), 127.0, 127.45, 127.9, 133.5 (q, $^{3}J_{CF}$ = 8 Hz, =$\underline{C}$HPh), 137.3, 138.25 (q, $^{2}J_{CF}$ =23 Hz, CF_3-$\underline{C}$); Anal. Calc. for $C_{13}H_{15}F_3$: C 68.3, H 6.5 ; Found C 68.2, H 6.75.

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(*Received in France* 4 *October* 1995; *accepted* 6 *November* 1995)