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Stereoselective Enolization of Methyl Dithiopropanoate by Adsorption on Alumina–Potassium Fluoride

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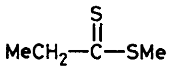
Alkylation of methyl dithiopropanoate with benzyl chloride at room temperature by adsorption on alumina–potassium fluoride is more selective than in solution under selected conditions (Pr^i_2NLi; −70 °C).

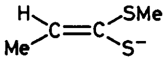
Reactions carried out *via* adsorption on inorganic solids[1] without solvent (dry reactions[2]) have recently received considerable attention. These reactions often involve milder conditions, easier work-up, and higher selectivity than similar reactions in solution.

Methyl dithiopropanoate (**1**) is an acidic (pK 11.4) equivalent of methyl propanoate.[3] The *cis*-selectivity of the kinetic deprotonation of dithiopropanoate is particularly interesting for the stereospecific aldol[4,5] and Michael reactions. Methyl dithiopropanoate (**1**) in the presence of a base gives a mixture of dithioenolates (**2a**) and (**2b**). With lithium as cation the *cis*-derivative (**2a**) is kinetically preferred.[4] The irreversible alkylation of the dithioenolates (**2a**) and (**2b**) with benzyl chloride gave information about the stereochemistry of dithioenolization. The ^1H n.m.r. spectra of the products (**3a**) and (**3b**) are different. Assignment was based on the favoured *cis*-kinetic dithioenolization of (**1**) in tetrahydrofuran (THF) with lithium di-isopropylamide (LDA)[4] [*Me*C, d, δ 1.60 for (**3a**) and 1.78 for (**3b**)]. In solution the effect of the cation is very important; with lithium (Table 1, entries 1 and 2) the reaction is stereoselective, but this is not the case with potassium (entries 3 and 4).

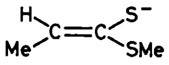


$$MeCH_2-\overset{\overset{\displaystyle S}{\|}}{C}-SMe$$

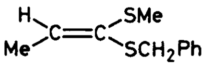
(1)



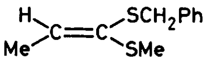
(2a)



(2b)



(3a)



(3b)

Dry reaction at room temperature (20 °C) with alumina is not selective (entry 5). With alumina–Bu^{t}OLi results are similar to those obtained in solution with lithium as cation (entry 6). Surprisingly with alumina–KF very good selectivity is observed (entry 7), in contrast with results observed in solution (entry 4).[6] Addition of solvents like acetonitrile (entry 8) has no effect on the stereoselectivity probably because the reaction takes place on the surface of the solid base and (**2a**) and (**2b**) are strongly adsorbed.

These observations suggest that adsorption of organic compounds without solvent on an inorganic support should provide a means of controlling stereoselectivity.

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Table 1. Alkylation of methyl dithiopropanoate (3 mmol) by benzyl chloride (3 mmol).

Entry	Base (equiv.)	Solvent	Conditions	(**3a**)/(**3b**)	% Yield of (**3**)
1	LDA (3)	THF	−70 °C; 3 h	70/30	70
2	Bu^{t}OLi (3)	THF	20 °C; 3 h	68/32	41
3	Bu^{t}OK (3)	THF	20 °C; 3 h	57/43	65
4	KF (10)	DMF^a	20 °C; 2 days 153 °C; 16 h	— 42/58	>2 95
5	Alumina (4 g) (Woelm N)	None	20 °C; 2 days	53/47	59
6	Alumina–Bu^{t}OLi (4 g; 10 equiv.)	None	20 °C; 2 days	67/33	81
7	Alumina–KF (4 g; 10 equiv.)^b	None	20 °C; 2 days	85/15^c	95^c
8	Alumina–KF (4 g; 10 equiv.)	MeCN (12 ml)	20 °C; 2 days	85/15	96

[a] DMF = dimethylformamide. [b] Alumina–KF samples containing 2—4.1% of water gave identical results (yield and stereochemistry). An endothermic peak was observed at 100—120 °C by differential thermal analysis (20—450 °C) attributed to water desorption. The amount of water adsorbed was determined by thermogravimetric analysis (20—200 °C). [c] Reproducibility was good in this experiment (5 experiments: yield ±5%, stereochemistry ±3%).