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Unexpected Heteroatom-Assisted C-4 Alkylation of a 1,3-Dioxolane

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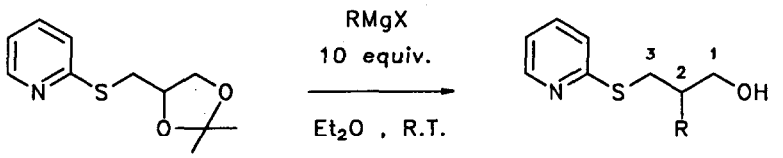
Key Words : Grignard reagent; cyclic ketal cleavage; aza-/thia-assistance

Abstract : *The reaction of a number of organomagnesium halides with a 4-(2-pyridyl)thiomethyl-1,3-dioxolane* **1** *mainly afforded C-branched pyridylthiopropanols* **2**. *These versatile synthons resulted from an atypical combined aza-/thia-assisted C-4 alkylation of the cyclic ketal system.*

In recent years, one of the most powerful methods for carbon-carbon bond formation has been the displacement of a nucleofugal group (*e.g.* halide, sulfonate...) by a carbon nucleophile of the organocopper reagent type[1]. In many cases however, substitution of a secondary carbon center has shown unpredictable reactivity patterns, thus calling for strategical modifications involving ligand-tailoring[2] or neighbouring heteroatom assistance[3].

On the other hand, the poor nucleofugal ability of alkoxy groups in the cleavage of acetals by organometallic reagents usually requires severe conditions and substitution - particularly in 1,3-dioxolanes - occurs through exclusive attack on the acetal carbon[4,5].

We now report the reaction of Grignard reagents on a 1,3-dioxolane bearing a (2-pyridyl) thiomethyl appendage on the C-4 position (i.e. **1**). In that case, a remote controlled nucleophilic substitution with simultaneous acetone elimination occurs on the more hindered **non-ketal carbon**, so that branched propan-1-ols **2** are formed in fair yields:



1 **2**

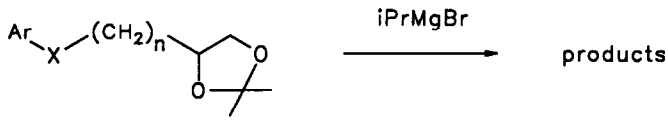
The following table shows the results for the reaction of miscellaneous Grignard reagents (5 to 10-fold excess in Et_2O or THF at room temperature) with ketal **1**, which had been readily obtained in *ca* 80% yield through direct coupling of 2,3-*O*-isopropylideneglycerol with 2-mercaptopyridine in Mitsunobu conditions[6,7].

When R = Et, Pr, iPr or *n*Bu, good C-4 substitution rates were attained, whereas lengthening of the alkyl chain resulted in rapid lowering of the yields through loss of reactivity.

Atypical methyl- and phenylmagnesium reagents only gave moderate yields of the corresponding primary alcohols **2a** and **2h**[8].

	R	yield %	Selected ^{1}H-NMR ($CDCl_3$ / 300 MHz) data H-1a(*dd*)	H-1b(*dd*)	H-2(*m*)	H-3a(*dd*)	H-3b(*dd*)
2a	Me	30	3.56	3.39	2.08	3.44	3.19
2b	Et	65	3.63	3.44	1.80	3.45	3.24
2c	Pr	64	3.61	3.43	1.90	3.47	3.23
2d	*i*Pr	67	3.75	3.53	1.59	3.47	3.33
2e	*n*Bu	63	3.61	3.43	1.88	3.45	3.24
2f	*n*-hexyl	24	3.58	3.40	1.88	3.43	3.20
2g	*n*-octyl	0	-	-	-	-	-
2h	Ph	40	3.93	3.88	3.16	3.67	3.56

In order to investigate the scope of this very unusual substitution and to try and elucidate how the aza-heterocycle interferes in the course of the reaction, we have studied the influence of three main parameters - Ar, n, X - as shown in the following scheme :



3 Ar = Ph X = S n = 1
4 Ar = Pyr X = S n = 2
5 Ar = Pyr X = S n = 4
6 Ar = Pyr X = CH_2 n = 1
7 Ar = Pyr X = O n = 1

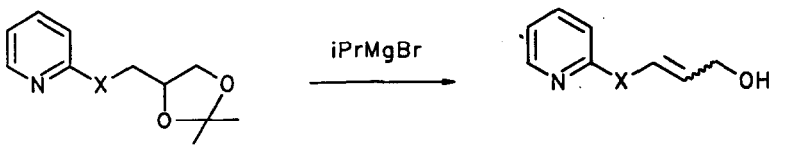
When submitted to the model-Grignard reagent iPrMgBr, ketal **3** (in which the heterocyclic moiety is replaced by a phenyl group[10]) showed no reaction. Such a result highlights the role of the aza-assistance of the heterocycle in the mechanistical process.

The influence of the distance between the nitrogen atom and the electrophilic acceptor site was then studied on ketals **4** (n = 2)[11] and **5** (n = 4)[12], both obtained from the corresponding primary alcohols *via* a Mitsunobu reaction[6].

In neither case did the expected substitution take place, thus showing the major importance of the molecular topology in the neighbourhood of the reactive site.

Finally, the critical role of the sulfur atom in the transformation of **1** into **2** was demonstrated when studying the reactivity towards an organo-magnesium reagent of the isosteric substrates **6** and **7**, which were synthesized according to published methods[13,14].

The carba-analog **6** showed no reaction with iPrMgBr, whereas the oxa-analog **7** solely underwent minor acetone elimination consecutive to the formation of a carbanion, producing - albeit in poor yield - *(E)*-3-(2-pyridyl)oxyprop-2-en-1-ol **8b** [15,16].



1 X = S
7 X = O

8a X = S
8b X = O

These preliminary results clearly demonstrate the particular importance of both the pyridyl moiety and the thiomethylene unit in this new C-alkylation of a 1,3-dioxolane. Studies are under way for an evaluation of miscellaneous aza-heterocyclic substituents and other cyclic ketals; on the other hand, focusing is concurrently brought on the stereochemical outcome of the substitution.

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REFERENCES AND NOTES

1. Posner, G.H. *Org. Reactions*, **1975**, *22*, 253-400.

2. (a) Lipshutz, B.H. *Synthesis*, **1987**, 325-41 and references cited.
(b) Lipshutz, B.H. *Synlett*, **1990**, 119-28.

3. Hanessian, S.; Thavonekham, B.; DeHoff, B. *J. Org. Chem.* **1989**, *54*, 5831-3.

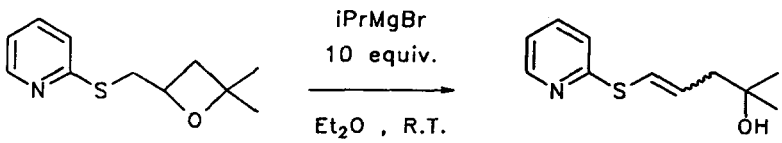
4. Trofimov, B.A.; Korostova, S.E. *Russ. Chem. Rev.* **1975**, *44*, 41-55.

5. Gelas, *J. Adv. Carbohydr. Chem. and Biochem.* **1981**, *39*, 71-156.

6. Besson, T.; Al Neirabeyeh, M.; Viaud, M.C.; Rollin, P. *Synth. Commun.* **1990**, *20*, 1631-9.

7. All new compounds were fully characterized spectroscopically (300 MHz ^{1}H-NMR) and gave correct M^+ by high resolution mass spectrometry.
Selected NMR data ($CDCl_3$) for compound **1** : 1.35 & 1.46 (2s, 6H, 2 Me); 3.32 (dd, 1H, J_{gem} = 13.6 Hz, J_{vic} = 6.8 Hz, H-3b); 3.50 (dd, 1H, J_{vic} = 5.6 Hz, H-3a); 3.79 (dd, 1H, J_{gem} = 8.4 Hz, J_{vic} = 6.0 Hz, H-1b); 4.10 (dd, 1H, J_{vic} = 6.0 Hz, H-1a); 4.39 (m, 1H, H-2).

8. On several occasions, the formation of an unexpected side-product, 4-methyl-1-(2-pyridyl)thiopent-1-en-4-ol **9** was observed. This compound should most likely result from Grignard-induced ring-cleavage[9] of 2,2-dimethyl-4-(2-pyridyl)thiomethyloxetane **10**, which could be formed *in situ* through reductive ring-contraction of dioxolane **1**.
Oxetane **10** was therefore synthesized from the hydroxymethyl precursor[17] by standard Mitsunobu thiofunctionalization[6] : reaction of **10** with excess iPrMgBr actually produced **9** in 65% yield.



Selected NMR data ($CHCl_3$) for compound **9** : 1.27 (s, 4.2H, *E*-Me); 1.29 (s, 1.8H, *Z*-Me); 2.40 (d, 1.4H, J_{vic} = 7.8 Hz, *E*-CH_2); 2.46 (d, 0.6H, J_{vic} = 7.7 Hz, *Z*-CH_2); 6.03 (dt, 0.3H, $J_{2,1}$ = 9.6 Hz, *Z*-H-2); 6.13 (dt, 0.7H, $J_{2,1}$ = 15.4 Hz, *E*-H-2); 6.64 (d, 0.7H, *E*-H-1); 6.96 (d, 0.3H, *Z*-H-1).

9. Stirling, C.J.M. *Tetrahedron* 1985, **41**, 1613-66.

10. Suk-Ku Kang; Dong-Soo Shin *Bull. Korean Chem. Soc.* 1986, **7**, 159-60.

11. Selected NMR data ($CHCl_3$) for **4** : 1.40 & 1.47 (2s, 6H, 2 Me); 1.98 (m, 2H, H-3a & H-3b); 3.17 (ddd, 1H, J_{gem} = 13.5 Hz, H-4b); 3.32 (ddd, 1H, H-4a); 3.61 (dd, 1H, J_{gem} = 6.6 Hz, J_{vic} = 6.0 Hz, H-1b); 4.08 (dd, 1H, J_{vic} = 6.0 Hz, H-1a); 4.25 (m, 1H, H-2).

12. Selected NMR data ($CHCl_3$) for **5** : 1.35 & 1.41 (2s, 6H, 2 Me); 1.40-1.65 (m, 4H, 4- & 5-CH_2); 1.76 (m, 2H, 3-CH_2); 3.18 (ft, 2H, J_{vic} = 7.2 Hz, 6-CH_2); 3.50 (ft, 1H, J_{vic} = 7.2 Hz, H-1b); 4.02 (ft, 1H, H-1a); 4.08 (m, 1H, H-2).

13. Bowman, R.E.; Evans, D.D. *J. Chem. Soc.* 1956, 2553-5.

14. McClure, D.E.; Engelhardt, E.L.; Mensler, K.; King, S.; Saari, W.S.; Huff, J.R.; Baldwin, J.J. *J. Org. Chem.* 1979, **44**, 1826-31.

15. Selected NMR data for **8b** : 4.22 (d, 2H, Jvic = 7.3 Hz, CH_2O); 5.67 (dt, $J_{2,3}$ = 12.5 Hz, H-2); 7.63 (d, 1H, H-1).

16. A similar elimination was occasionally observed as a side reaction in the case of ketal **1**, thus resulting in *(E/Z)*-3-(2-pyridyl)thioprop-2-en-1-ols **8a**.
Selected NMR data ($CHCl_3$) for compound **8a** : 4.28 (bd, 1.4H, J_{vic} = 5.9 Hz, *E*-CH_2); 4.36 (bd, 0.6H, J_{vic} = 6.4 Hz, *Z*-CH_2); 6.09 (dt, 0.3H, $J_{2,3}$ = 9.7 Hz, *Z*-H-2); 6.17 (dt, 0.7H, $J_{2,3}$ = 15.6 Hz, *E*-H-2); 6.98 (d, 0.3H, *Z*-H-1); 7.02 (d, 0.7H, *E*-H-1).

17. Bats, J.P.; Moulines, J.; Picard, P.; Leclercq, D. *Tetrahedron* 1982, **38**, 2139-46.

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