Tetrahedron Letters Vol. 22, pp 1101 - 1104 0040-4039/81/0315-1101$02.00/0

RETENTION OF CONFIGURATION IN LEWIS ACID MEDIATED α-ALKYLATION OF CARBONYL COMPOUNDS USING S_N1 REACTIVE ALKYL HALIDES

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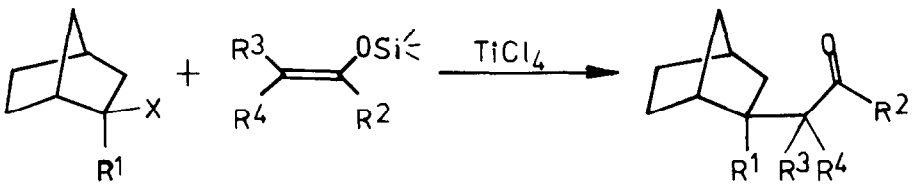
Summary: Certain S_N1 reactive alkyl halides undergo C-C bond formation in Lewis acid induced α-alkylations of carbonyl compounds with formal retention of configuration.

The alkylation of carbanions such as enolates using alkyl halides usually proceeds via an S_N2 mechanism and therefore yields products with inversion of configuration. We wish to report that S_N1 reactive alkyl halides known to solvolyze stereoselectively due to anchimeric assistance and/or other factors [1] can be induced to undergo C-C bond formation with complete retention of configuration. To achieve this end, the strongly basic classical enolates must be replaced by weakly basic carbon nucleophiles in Lewis acidic medium. [2]

As a first example, we have found that exo-2-norbornylhalides 1a-b react with various silyl enol ethers 2 in the presence of $TiCl_4$ to afford the α-alkylated ketones 3 having the carbonyl function solely in the exo position [3] (Table 1).



1 2 3

a) $R^1 = H$, $X = Br$
b) $R^1 = CH_3$, $X = Cl$

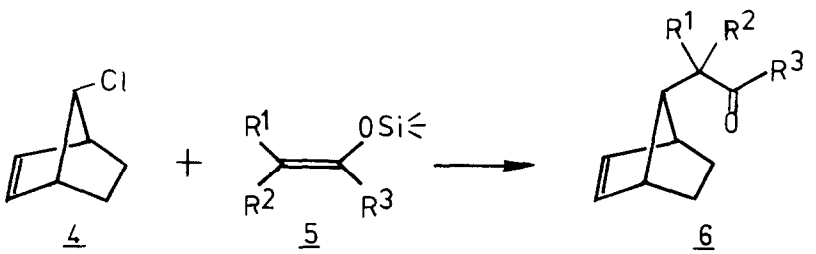
Table 1. Norbornylation of Ketones [a]

Alkylating agent	Product 3	Yield [b] of 3 (%)
1a	$R^1 = R^4 = H$; $R^2 = CH_2CH_3$; $R^3 = CH_3$	40 (74)
1a	$R^1 = R^3 = R^4 = H$; $R^2 = C(CH_3)_3$	73
1a	$R^1 = R^3 = R^4 = H$; $R^2 = CH_2C(CH_3)_3$	48 (70)
1a	$R^1 = H$; $R^2 = CH(CH_3)_2$; $R^3 = R^4 = CH_3$	61
1b	$R^1 = R^3 = CH_3$; $R^2 = CH_2CH_3$; $R^4 = H$	90
1b	$R^1 = CH_3$; $R^2 = C(CH_3)_3$; $R^3 = R^4 = H$	66
1b	$R^1 = CH_3$; $R^2,R^3 = -(CH_2)_3-$; $R^4 = H$	65
1b	$R^1 = CH_3$; $R^2,R^3 = -(CH_2)_4-$; $R^4 = H$	78

a) In case of 1a : equivalent amounts of $TiCl_4$ for 3-5 h at -30° C according to the procedure described in ref. [4]; in case of 1b similar procedure at -78° C for 3 h.

b) The numbers refer to isolated products (distillation or chromatography) in analytically pure form; the numbers in brackets refer to conversion as determined by ^{1}H-NMR.

We have also studied anti-7-chloronorbonene (4), a system which is known to display unusually high solvolysis rates as well as stereoselectivity.[5] In our case $TiCl_4$ or ZnI_2 promoted C-C bond formation affords high yields of products 6 having the norbornene skeleton with the carbonyl function solely in the anti position, [6] i.e., with complete retention of configuration (Table 2).



4 5 6

Table 2. Norbornenylation of Ketones and Esters

Lewis acid [a]	Temp./ Time	Product 6	Conversion (%)
$TiCl_4$	-30° C/ 5 h	$R^1 = R^2 = H$; $R^3 = C(CH_3)_3$	85
$ZnCl_2$	22° C/ 24 h	as above	45
ZnI_2	22° C/ 6 h	as above	95 [b]
ZnI_2	22° C/ 8 h	$R^1 = H$; $R^2 = CH_3$; $R^3 = CH_2CH_3$	95 [b]
ZnI_2	22° C/ 14 h	$R^1 = H$; $R^2 = CH_3$; $R^3 = OCH_3$	95 [b]
ZnI_2	22° C/ 14 h	$R^1 = R^2 = CH_3$; $R^3 = OCH_3$	95 [b]

a) Equivalent amounts of Lewis acid in CH_2Cl_2.

b) Following aqueous workup and treatment with charcoal the products are 95 % pure as checked by VPC; for analytical purposes small portions were chromatographed using silica gel and pet. ether (40-60° C)/ether.

Several features in the above system deserve mention. Firstly, the reactions are considerably faster using ZnI_2 than $ZnCl_2$. This may be due to rapid Cl/I exchange at C^7, rendering the system more reactive during alkylation. Secondly, no tricyclic products are formed under the (presumably) irreversible conditions of C-C bond formation. In solvolyses, buffered solutions afford mostly norbornene products with the anti-7-configuration, while those having high methoxide ion concentrations yield 1:1 mixtures of norbornene and tricyclo [4,1,0,$0^{3,7}$] heptane derivates. [5] Thus, our conditions appear to be more comparable to the former case.

Finally, the above stereoselective reactions are of potential synthetic value. For example, oxidative cleavage of the C-C double bond in compounds 6 should yield tri-substituted cyclopentane derivatives with complete control of relative stereochemistry.
We believe that other S_N1 reactive alkyl halides which are known to solvolyze stereoselectively are also likely to be useful alkylating agents.

This work was supported by the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft.

References and Notes:

1) B. Capon and S.P. Mc Manus, Neighboring Group Participation, Vol. I, Plenum Press, N.Y. 1976; C.A. Grob and A. Waldner, Tetrahedron Lett. 1980, 4433.

2) Lewis acid mediated α-alkylations of ketones: M.T. Reetz and S. Hüttenhain, Synthesis 1980, 941, and ref. cited therein; T.H. Chan, I. Paterson and J. Pinsonnault, Tetrahedron Lett. 1977, 4183.

3) The exo assignment is based on ^{13}C-NMR-data (γ effects at C^6 and C^7; M. Sauerwald, Diplomarbeit, Univ. Marburg 1980). In relevant cases in Table 1 the product exists as a diastereomeric pair, each exo.
^{13}C-NMR($CDCl_3$, δ, TMS): 3a: 215.90, 215.59, 52.12, 52.03, 45.23, 40.22, 38.40, 37.15, 36.70, 35.67, 34.97, 34.57, 30.35, 28.69, 16.82, 14.78, 7.71; 3b: 215.54, 43.96, 43.79, 41.33, 38.39, 37.03, 36.77, 35.38, 29.97, 28.58, 26.40; 3c: 210.70, 55.10, 52.50, 41.27, 37.35, 36.78, 35.35, 31.04, 30.10, 29.94, 29.80, 28.60; 3d: 220.20, 51.08, 47.39, 38.30, 36.99, 36.19, 34.12, 33.99, 32.08, 28.06, 21.20, 21.04, 20.42; 3e: 215.64, 215.52, 53.35, 52.74, 45.89, 45.50, 44.76, 44.56, 42.96, 41.93, 38.18, 38.07, 37.94, 37.73, 37.29, 28.14, 27.78, 24.96, 24.39, 19.85, 18.57, 13.97, 12.11, 7.59, 7.46; 3f: 215.39, 48.11, 46.27, 46.12, 44.45, 38.72, 38.01, 28.05, 26.33, 24.36, 23.66; 3g: 221.54, 220.18, 57.64, 56.57, 45.51, 45.12, 43.82, 42.03, 41.66, 40.68, 40.20, 38.49, 37.87, 37.66, 28.29, 28.14, 26.33, 25.63, 24.55, 24.32, 20.01, 19.45, 19.21; 3h: 212.81, 212.31, 60.04, 58.96, 47.34, 45.74, 44.05, 43.42, 40.99, 40.38, 38.23, 37.92, 30.79, 29.04, 28.44, 27.74, 26.26, 26.11, 24.95, 24.29, 19.70, 19.05; 6a: 214.87, 137.00, 53.37, 44.04, 35.96, 26.26, 21.76; 6b: 214.51, 137.32, 136.14, 61.01, 45.55, 43.07, 42.30, 34.51, 21.96, 21.57, 15.24, 7.51; 6c: 176.44, 137.25, 136.16, 61.50, 51.25, 43.56, 42.26, 38.89, 21.79, 21.47, 15.29; 6d: 177.61, 138.67, 67.29, 51.43, 42.85, 42.33, 25.53, 22.60 ppm.

4) M.T. Reetz and W.F. Maier, Angew. Chem. 90, 50 (1978); Angew. Chem. Int. Ed., Engl. 77, 48 (1978).

5) A. Diaz, M. Brookhart and S. Winstein, J. Am. Chem. Soc. 88, 3133, 3135 (1966).

6) The assignment is based upon ^{1}H-NMR-data, i. e., anti-7-H is known to show pronounced long range coupling with the olefinic protons, while syn-7-H does not; see for example E.I. Snyder and B. Franzus, J. Am. Chem. Soc. 86, 1166 (1964).

(Received in Germany 18 December 1980)