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α-ALKYLATION OF CARBONYL COMPOUNDS USING 1-ACETOXY-1-FERROCENYLETHANE *

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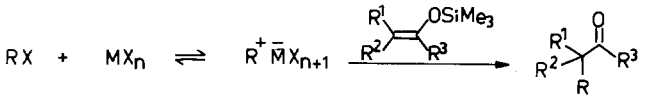
Summary

1-Acetoxy-1-ferrocenylethane reacts with ZnX_2 to form the corresponding secondary carbocation, which adds to the double bond of enoxysilanes derived from ketones, carboxylic acid esters, or lactones. This C–C bond-forming reaction provides an extremely mild and efficient way of alkylating carbonyl compounds at the α-position to form novel ferrocene derivatives.

Introduction

The α-alkylation of carbonyl compounds is usually brought about by the reaction of the corresponding lithium enolates with S_N2 active alkyl halides [1]. This synthetically useful C–C bond forming process is normally restricted to primary and certain secondary alkyl halides. Base sensitive secondary or tertiary derivatives cannot be used because HX-elimination takes place [1]. In order to get around this limitation, the concept of Lewis acid promoted alkylation of enoxysilanes using S_N1-active alkylating agents was introduced [2]. It became clear that essentially all alkylating agents which are more S_N1 active than isopropyl halides are potential reagents for the reaction. Alkyl halides in which neighboring group effects can operate are also useful alkylating agents [2,3]. Kinetic data from solvolyses can, in fact, be used as an aid in deciding whether a given alkyl halide is likely to be an active alkylating agent. In most of these cases use of lithium enolates fails to promote C–C bond formation, which means that the two procedures are complementary [2].



* Dedicated to Professor Jean Tirouflet on the occasion of his retirement.

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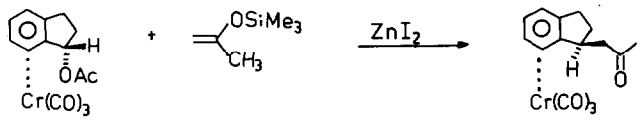
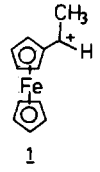
Another important advance in this area was the discovery that many alkyl halides can be replaced by the corresponding acetates, the latter being readily available from the alcohols [4]. This approach has been applied successfully in the synthesis of thienamycin by the Merck group [5], as well as in the stereoselective alkylation of enoxysilanes using tricarbonylchromium complexes of secondary benzyl acetates, a reaction that involves intermediate chromium-stabilized secondary carbocations [6]:



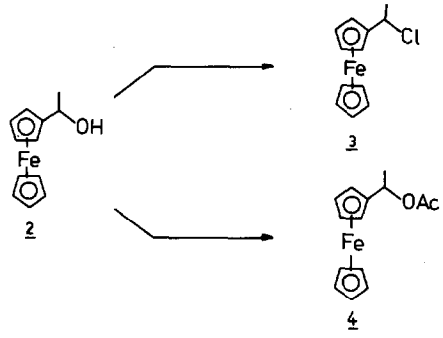
In view of the above, we thought it likely that ferrocenyl-substituted carbocations of type **1** would undergo similar C–C bond forming reactions; the ready formation and the stability of such cations are well documented [7]. This paper describes our efforts to induce these base-sensitive intermediates to react with enoxysilanes derived from ketones, esters, and lactones.



1

Results and discussion

The alcohol **2** was made from the readily available acetylferrocene and was converted into the chloride **3** and the acetate **4** by standard procedures [8].



2 3 4

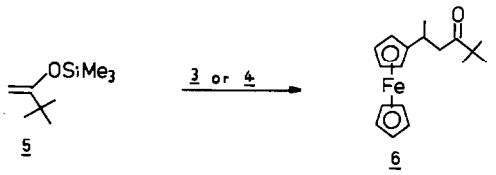
With the enoxysilane **5**, prepared from pinacolone, as substrate, a number of optimization experiments were performed using the mild Lewis acids ZnX_2 (Table 1). Chloride **3** was found to be an extremely reactive compound; in the presence of about 30 mol% $ZnCl_2$ all of it reacted within 30 minutes, but the yield of the desired product **6** was less than 30%, the rest consisting of an extremely viscous (polymeric?) material. The results of the reactions of the acetate were more promising. Use of one equivalent of ZnI_2 as the Lewis acid (which had previously been shown to be effective in alkylations of other acetates [4,6]) gave > 95% of **6**. A similar result was obtained when only catalytic amounts of ZnI_2 were used. The crystalline

TABLE 1

OPTIMIZATION OF THE REACTION **5** → **6** IN CH_2Cl_2

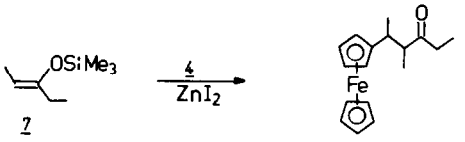
Alkylating agent	Lewis acid (mol%)	Temperature (°C)	Time (h)	Conversion to **6** (%)
3	$ZnCl_2$ (30)	−78	0.5	< 30
4	ZnI_2 (100)	+22	2	> 95
4	ZnI_2 (30)	+22	2	> 95

brown-orange product **6** was isolated analytically pure (in 90% yield) by passage through a short silica gel column with a petroleum ether/diethyl ether mixture as eluant.

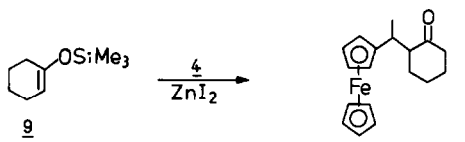


5 6

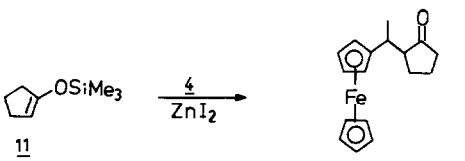
In the light of the above results, we proceeded to the alkylation of enoxysilanes, **7**, **9**, and **11**, at room temperature in the presence of 30 mol% ZnI_2. Excellent isolated yields were obtained in all cases, and so the method appears to be general. Owing to the prochirality of the enoxysilanes, the products can be formed as diastereomers, as is indeed observed (1/1 mixtures).



7 8 (89%)

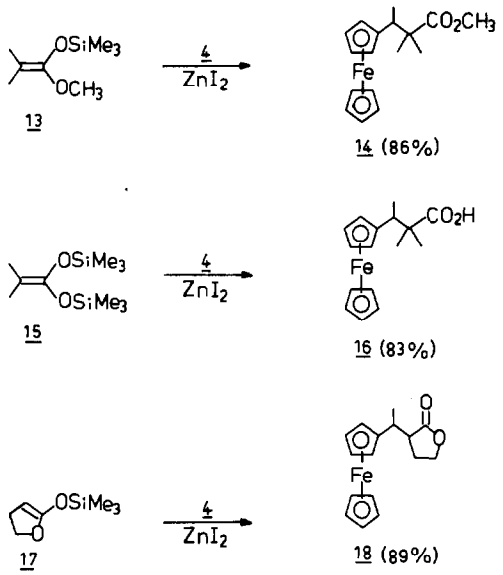


9 10 (82%)



11 12 (77%)

Extension of the method to the O-silyl ketene ketals **13**, **15** and **17** did not give rise to problems.



In summary, the ZnI_2-mediated alkylation of enoxysilanes with 1-acetoxy-1-ferrocenylethane (**4**) provides a mild and efficient method for C–C bond formation. Carbocations **1** are probably the intermediates which add to the electron rich double bond of the enolsilanes. (Deprotonation to form vinylferrocene, a potential side reaction, is not observed.) The novel ferrocene derivatives thus obtained are unlikely to be easily accessible by other routes.

Experimental

General

All reactions were performed in dry flasks under nitrogen. The following instruments were used in the analysis of the products. IR: Perkin–Elmer 457. ^1H NMR: Varian T60 and JEOL JNM-FX 100. ^{13}C NMR: Varian CFT20 and XL100. Elemental analyses were carried out by the Analytical Service of the Fachbereich Chemie Marburg and in the Mikroanalytische Labor Beller (Göttingen). The melting points are uncorrected.

General alkylation procedure

A dry 100 ml flask equipped with a nitrogen inlet is charged with anhydrous ZnI_2 (0.5 g, 1.6 mmol). The flask is evacuated and carefully heated with a Bunsen burner until the ZnI_2 sublimes on to its walls. After cooling, the ZnI_2 is scraped down with a spatula under nitrogen. About 40 ml of dry dichloromethane is added, followed by 5 mmol of an enoxysilane [9] and 1.36 g (5 mmol) of 1-acetoxy-1-ferrocenylethane (**4**) [8]. After 3 h stirring at room temperature the mixture is added to 200 ml of water. After two extractions with 50 ml portions of dichloromethane the combined extracts are washed with 50 ml of saturated $NaHCO_3$ solution then 50 ml of water, then dried over $MgSO_4$. The solvent is then removed and the residue purified by chromatography on a short silica gel column using 50/1 petroleum ether (40–60)/diethyl ether as eluant.

2,2-Dimethyl-5-ferrocenyl-hexan-3-one (6). 1.4 g (90%) of a solid, m.p. 46–47 °C. Found: C, 68.94; H, 7.75. $C_{18}H_{24}FeO$ calcd.: C, 69.24; H, 7.75%. IR (KBr): 3100, 2970, 2950, 2930, 1695, 1470, 1370, 1350, 1205, 1070, 1000, 900, 820, 810 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.08 (s, 9H), 1.20 (d, J 7 Hz, 3H), 2.56–2.63 (m, 2H), 3.10 (m, 1H), 4.05 (s, 4H), 4.11 (s, 5H) ppm. ^{13}C NMR ($CDCl_3$): δ 214.7, 95.1, 68.4, 67.0 (2 peaks), 65.7, 46.1, 44.1, 28.5, 26.1, 20.5 ppm.

5-Ferrocenyl-4-methyl-hexan-3-one (8). 1.32 g (89%) of a brown oil (1/1.3 mixture of diastereomers). Found: C, 68,71; H, 7.59. $C_{17}H_{22}FeO$ calcd.: C, 68,47, H, 7.44%. IR (Film): 3100, 2980, 2940, 2880, 1710, 1460, 1410, 1380, 1355, 1105, 1020, 1000, 970, 910, 820 cm^{-1}. ^1H NMR (CCl_4): δ 0.8–1.2 (m), 1.2–1.4 (m), 2.0–3.0 (m), 3.9–4.3 (m) ppm. ^{13}C NMR ($CDCl_3$): δ 215.0/214.9, 93.5/92.3, 68.7, 68.4, 68.0, 67.4, 66.9, 65.6, 53.6/53.4, 36.1/35.8, 35.6, 18.0, 15.9, 14.8, 12.8, 7.5 ppm.

2-(1-Ferrocenyl-ethyl)cyclohexanone (10). 1.27 g (82%) of a solid, m.p. 70–73 °C (1/1.2 mixture of diastereomers). Found: C, 69.63; H, 7.29. $C_{18}H_{22}FeO$ calcd.: C, 69.69; H, 7.15%. IR (KBr): 3080, 2930, 2860, 1700, 1460, 1450, 1310, 1120, 1100, 1020, 1000, 910, 890, 835, 815, 800 cm^{-1}. ^1H NMR (CCl_4): δ 1.3 (d, J 8 Hz), 1.4 (d, J 7 Hz), 1.5–2.6 (m), 3.1–3.6 (m), 4.0–4.3 (m) ppm. ^{13}C NMR ($CDCl_3$): δ 215.8/211.8, 94.0/92.4, 69.3, 68.5, 67.3, 67.1, 66.7, 66.0, 58.0/57.8, 42.0, 31.4, 31.0, 30.4, 27.6, 27.1, 26.8, 24.9, 24.3, 19.1, 14.7 ppm.

2-(1-Ferrocenyl-ethyl)cyclopentanone (12). 1.14 g (77%) of a brown oil (1/1.2 mixture of diastereomers). Found: C, 68.86; H, 6.98. $C_{17}H_{20}FeO$ calcd.: C, 68.94; H, 6.81%. IR (Film): 3095, 2960, 2870, 1735, 1470, 1450, 1405, 1370, 1270, 1155, 1105, 1040, 1020, 1000, 920, 820 cm^{-1}. ^1H NMR (CCl_4): δ 1.1 (d, J 7 Hz), 1.4 (d, J 7 Hz), 1.5–2.3 (m), 3.0–3.4 (m), 3.7–4.1 (m) ppm. ^{13}C NMR ($CDCl_3$): δ = 221.1/219.9. 93.6/90.9, 69.3, 69.0, 68.4, 68.1, 67.4, 67.1, 67.0, 66.7, 66.5, 66.1, 56.2/55.6, 39.2/39.0, 33.0, 32.0, 24.0, 23.6, 20.4, 18.8, 15.1 ppm.

3,3-Dimethyl-2-ferrocenyl-butanoic acid methylester (14). 1.35 g (86%) of a solid, m.p. 80–81 °C. Found: C, 64.77; H, 6.92. $C_{17}H_{22}FeO_2$ calcd.: C, 64.98; H, 7.06%. IR (KBr): 3095, 2980, 2940, 2900, 1730, 1460, 1450, 1300, 1250, 1130, 1100, 1030, 1000, 850, 820, 815, 805 cm^{-1}. ^1H NMR (CCl_4): δ 0.8 (s, 6H), 1.2 (d, J 7 Hz, 3H), 3.0 (q, J = 7 Hz, 1H), 3.6 (s, 3H), 3.8–4.1 (m, 9H) ppm. ^{13}C NMR ($CDCl_3$): δ 178.5, 90.6, 69.2, 68.5, 67.0, 66.7, 51.5, 46.7, 40.5, 22.9, 20.8, 15.5 ppm.

3,3-Dimethyl-2-ferrocenyl-butanoic acid (16). 1.25 g (83%) of a solid, m.p. 150 °C, isolated by the usual chromatographic procedure but with 5/1 petroleum ether (40–60)/diethylether as the eluant. Found: C, 63.94; H, 6.77. $C_{16}H_{20}FeO_2$ calcd.: C, 64.02; H, 6.72%. IR (KBr): 3300–2400, 1700, 1465, 1410, 1300, 1280, 1180, 1140, 1105, 1060, 1030, 1000, 930, 845, 830, 810 cm^{-1}. ^1H NMR (CCl_4): δ = 1.0 (s, 6H), 1.4 (d, J 7 Hz, 3H), 3.0 (q, J 7 Hz, 1H), 4.0–4.3 (m, 9H) ppm, carboxy-proton not visible. ^{13}C NMR ($CDCl_3$): δ 184.9, 90.4, 69.5, 68.6, 67.11, 67.07, 66.8, 46.6, 40.3, 23.0, 20.6, 16.0 ppm.

3-(1-Ferrocenyl-ethyl)dihydrofuran-2-one (18). 1.33 g (89%) of a brown oil (1/1.4 mixture of diastereomers), isolated in the same way as compound **16**. Found: C, 64.51; H, 6.15; $C_{16}H_{18}FeO_2$ calcd.: C, 64.45; H, 6.09%. IR (Film): 3095, 2970, 2900, 2880, 1770, 1450, 1375, 1215, 1160, 1105, 1025, 1000, 940, 820 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.26 (d, J 7 Hz), 1.40 (d, J 7 Hz), 1.83 (m), 2.04 (m), 2.64 (m), 2.78 (m), 3.28 (m), 3.71 (m), 4.00–4.24 (m) ppm. ^{13}C NMR ($CDCl_3$): δ 178.9/178.10, 91.94/89.13, 68.49, 68.31, 68.22, 67.90, 67.44, 67.13, 67.02, 66.62, 66.47, 66.21, 65.96, 46.37/46.18, 33.53/32.86, 23.17/23.07, 18.75/14.87 ppm.

Acknowledgement

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