

NUCLEOPHILIC REACTIONS IN STRONGLY ACIDIC MEDIA.

HIGHLY SPECIFIC HOMOLYTIC AROMATIC ALKYLATION AND ACYLATION

Laily Bin Din, Otto Meth-Cohn* and Nigel D.A. Walshe

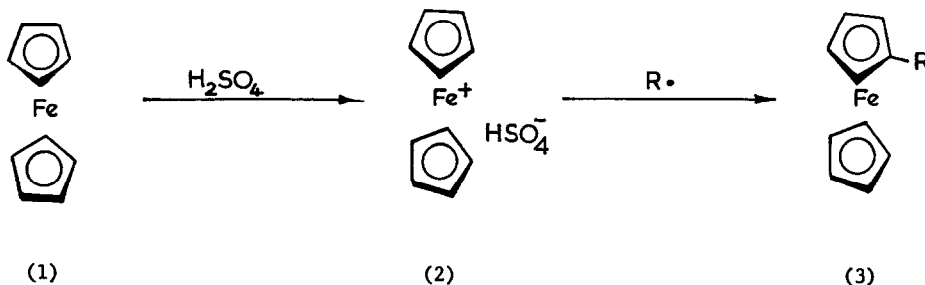
The Ramage Laboratories, Department of Chemistry and Applied Chemistry,

University of Salford, Salford M5 4WT, England

Under Minisci reaction conditions, nucleophilic carbon free radicals readily substitute ferrocene (as the ferricinium ion) and protonated acetophenone, the latter reaction being highly positionally specific.

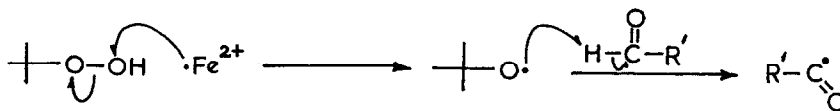
The Minisci reaction¹ (i.e. the action of nucleophilic carbon free radicals on protonated π -deficient N-heteroaromatics) allows highly specific alkylation and acylation of heteroaromatic bases which are otherwise inert to the Friedel-Crafts reaction. As such it is a major synthetic development in heterocyclic chemistry. We herein demonstrate that the principle may also be applied in the homocyclic series. We have studied two representative systems (a) ferrocene (Fc) and (b) acetophenone.

Probably all the known classical homolytic substitutions of ferrocene (1) involve initial formation of the ferricinium ion (2)², easily made by oxidation with cold H_2SO_4 . Homolytic alkylation and acylation of ferrocene is not reported but is easily accomplished

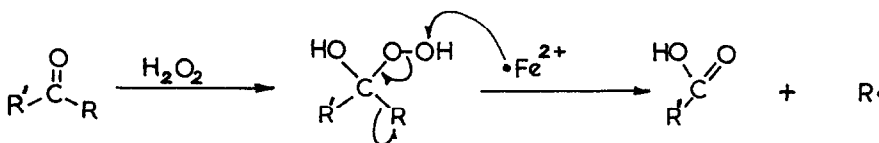


using the ion (2), in moderate yield. Thus acetylation and benzoylation are rapidly conducted using acyl radicals produced as in Scheme 1 from an aldehyde. Introduction of the COOR group and alkyl groups is easily achieved from a ketone by treatment with

H_2O_2 and Fe^{2+} (Scheme 2).



Scheme 1



Scheme 2

Some typical results are summarised in Table 1.

Table 1

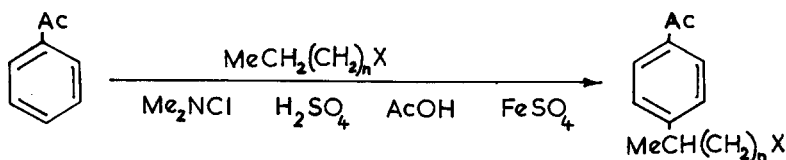
Rad. Source	Radical	R * Fc	Temp (°C)	Reaction Time (min)	Product (3)			Rcvd. Fc (%)
					% [¶]	m.p.	lit. m.p. ²	
MeCHO	·COMe	2	-12	10	25(100)	84	83-4	75
					36(53)	84	83-4	32
PhCHO	·COPh	6	-12	10	33	110	111.5-12	3
AcCO ₂ Me	·CO ₂ Me	4	0	60	23 [†]	70	70-1	0
Ac(CH ₂) ₂ CO ₂ H	·(CH ₂) ₂ CO ₂ H	4	0-10	10	24	120	119-20	0
Ac(CH ₂) ₃ CO ₂ H	·(CH ₂) ₃ CO ₂ H	2	0-10	5	12(28)	117-20	117-8	38
(CH ₂) ₅ CO	·(CH ₂) ₅ CO ₂ H	2	-12	10	28(42)	90	91.5-92.5	33

* Molar ratio of radical to ferrocene. [¶] Yield based on starting ferrocene; figure in brackets indicate yield from consumed ferrocene. [†] Also, 1,1'-disubstituted product (54%, m.p. 113-4°, lit.² m.p. 114-5°) produced. All the reactions were conducted using Fc (0.01 M) in H_2SO_4 (5 ml) diluted with water (15 ml) and AcOH (15 ml), to which the radical source and ferrous sulphate solution were separately added at equivalent rates.

Although the yields are not high the method is very simple and quick giving products generally only available in multi-step reactions.

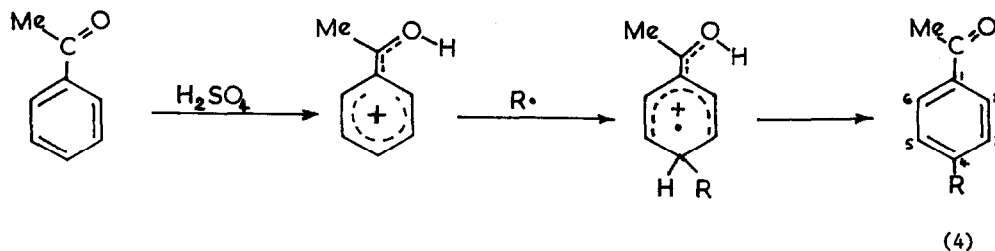
The second substrate, acetophenone, requires strong acid to allow protonation. Reactions were thus conducted in concentrated H_2SO_4 or 25% oleum containing acetic acid (Scheme 3). Radicals were generated using electrophilic aminium radicals³ ($\text{Me}_2\text{NH}^\cdot$) generated from chlorodimethylamine and FeSO_4 to abstract a hydrogen atom from an aliphatic compound RH. The reaction is remarkably specific in two senses: (a) Substitution of the acetophenone occurs predominately in the para position, as borne out by p.m.r., c.m.r., m.s., h.p.l.c. and unambiguous synthesis of the products (4)⁴; (b) Radicals, R^\cdot are only produced when at least a four carbon chain is attached to a function (RX) and predominately occurs at the penultimate carbon (giving $\text{CH}_3\dot{\text{C}}\text{H}(\text{CH}_2)_n\text{X}$)³. The total impurity in the products amounts to only a few percent.

Table 2



$\text{CH}_3\text{CH}_2(\text{CH}_2)_n\text{X}$ n X	Temp. (°C)	Conversion PhAc (%)	Yield* (%)
2 Br	0-15	17	17
2 CO_2H	35-40	30	17
3 Br	0-15	15	44
3 CO_2H	35-40	38	43
3 CO_2H	45-50	35	52
3 CO_2H	0-15	23	58
3 OAc	0-15	37	16
4 Br	0-15	17	53

* Yields based on consumed acetophenone. Typical conditions: Me_2NCl (0.04 M) in 25% oleum (30 ml) added dropwise to a mixture of 25% oleum (30 ml), AcOH (20 ml), PhAc (0.04 M) and FeSO_4 hydrate (0.04 M) with stirring. After 2 h the mixture was poured onto ice, extracted and the product obtained by distillation.



Scheme 3

We thank the Malaysian Government and the S.R.C. for grants to LBD and NDAW, respectively.

References

1. F. Minisci, *Synthesis*, 1973, 1; F. Minisci and O. Porta, *Adv. Heterocyclic Chem.*, 1974, **16**, 123; F. Minisci, *Topics in Current Chem.*, 1976, **62**, 1.
2. M. Rosenblum, 'Chemistry of Iron Group Mettalloenes' Part 1. Interscience - John Wiley and Sons, New York, 1965; E.G. Perevalova and T.V. Nikitina in 'Organometallic Reactions', eds. E.I. Becker and M. Tsutsui, Wiley - Interscience, New York, 1972, **4**.
3. Y.L. Chow, W.C. Danen, S.F. Nelsen and R.H. Rosenblatt, *Chem. Rev.*, 1978, **28**, 243.
4. The series (4) $R = -(CH_2)_5COOMe$, $R = CH_3\overset{1}{CH}(CH_2)_3COOMe$ and $R = CH_3CH_2\overset{1}{CH}(CH_2)_2COOMe$ were synthesised by acetylation of 6-, 5-, and 4-phenylhexanoic acids and compared with the product derived from hexanoic acid and acetophenone after methyl ester formation, which showed the following properties: i.r. (liquid film): 1740 (CO_2Me), 1690 cm^{-1} ($COMe$); p.m.r. ($CDCl_3$) δ 7.90d (H-2,6), 7.27d (H-3,5), 3.63s (OMe), 2.5-3.1m (CH), 2.56s ($COMe$), 2.26t (CH_2CO), 1.58m (CH_2CH_2), 1.24d ($MeCH$); c.m.r. ($CDCl_3$) δ 195.61s ($COMe$), 172.11s (COO), 151.82s (C-1), 134.64s (C-4), 127.55d (C-3,5), 126.11 (C-2,6), 49.91q (OMe), 38.69d (CH), 36.37t (CH_2CH), 32.75t (CH_2CO), 25.01q ($COMe$), 22.06q ($MeCH$), 20.73t ($CH_2CH_2CH_2$). M.s.: m/e 248 (32%, M^+), 233 (5%, M^+-Me), 217 (2%, M^+-OMe), 175 (7%, $M^+-CH_2CO_2Me$), 161 (38%, $M^+-(CH_2)_2CO_2Me$), 147 (48%, $M^+-(CH_2)_3CO_2Me$), 145 (26%, $147-H_2$), 43 (100%, $MeCO$).

(Received in UK 26 September 1979)