Tetrahedron. Vol. 29, pp. 3979 to 3983. Pergamon Press 1973. Printed in Great Britain

REACTIONS OF ORTHO OXY-SUBSTITUTED BENZYL AND PHENACYL BROMIDES IN DIMETHYL SULPHOXIDE

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(*Received in the UK 27 June* 1973; *Accepted for publication 23 July* 1973)

Abstract—*o*-Acetoxy- and *o*-benzoyloxy-benzyl bromides and tosylates oxidatively rearrange in moist dimethyl sulphoxide to *o*-hydroxybenzyl esters; *o*-acetoxy- and *o*-benzoyloxy- phenacyl bromides rearrange to mixtures of 2-hydroxycoumaran-3-ones and *o*-hydroxyphenacyl esters; *o*-hydroxyphenacyl bromides also yield 2-hydroxycoumaran-3-ones, together with *o*-hydroxyphenacyl alcohols. 2-Acetoxybenzaldehyde is reductively rearranged by sodium borohydride to *o*-hydroxybenzyl acetate.

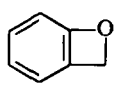
Since Kornblum, Jones, and Anderson[1] found, in 1959, that benzyl tosylates are readily oxidised to benzaldehydes by sodium hydrogen carbonate in anhydrous[2] dimethyl sulphoxide (DMSO) there have been reports[3] that benzyl halides react similarly. When studying the use of ortho oxy-substituted benzyl bromides as possible precursors of the unknown benzoxetene **1** we found,[4] from work involving the addition of aqueous reagents to DMSO solutions of these bromides, that they are reactive towards aqueous DMSO.

2-Acetoxybenzyl bromide **2a**, in moist DMSO, oxidatively rearranged after three days at room temperature to a mixture of 2-hydroxybenzyl acetate **3a** and 5-bromo-2-hydroxybenzyl acetate **3b**. The former is almost certainly the initial product, being halogenated in part by bromine slowly formed from the reaction[5] of the liberated bromide with DMSO. The reaction rate was greatly increased by first converting the benzyl bromide into 2-acetoxy-benzyl tosylate **2b** and no nuclear halogenated, secondary product was isolated. Only the latter **3b**, however, was obtained when 2-acetoxybenzyl bromide **2a** was *heated* in DMSO. Changing bromine for the poorer acetoxyl leaving group completely suppressed the reaction; 2-acetoxybenzyl acetate **2c** was recovered unchanged from DMSO even after being heated at 120–125°.

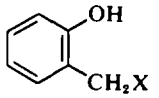
2-Acetoxy-5-bromobenzyl bromide **4a** and tosylate **4b** were readily converted into 5-bromo-2-hydroxybenzyl acetate **3b**. Benzoates were similarly reactive; 2-benzoyloxy-5-bromobenzyl bromide **4c** oxidatively rearranged to 5-bromo-2-hydroxybenzyl benzoate **4d**.

Wakselman,[6] and Helferich and von Blumencron,[7] have shown that *o*-acyloxybenzyl alcohols rearrange readily in mild base or acid conditions to benzyl esters. It appeared, therefore, that in the present work the *o*-acyloxybenzyl bromides might have been hydrolysed to the corresponding benzyl alcohols which, in the presence of liberated hydrogen bromide, would undergo the ester interchange reaction. An attempt to prepare 2-acetoxybenzyl alcohol, for a study of its reactions in DMSO, was unsuccessful. The reduction of 2-acetoxybenzaldehyde **5** by sodium borohydride gave the reductively rearranged ester, 2-hydroxybenzyl acetate **6**.

The possibility of initial benzyl alcohol formation was discounted when 4-acetoxybenzyl bromide **7a**

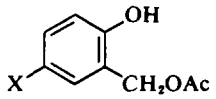


1



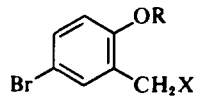
2

a: X = Br
b: X = OTs
c: X = OAc



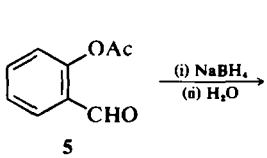
3

a: X = H
b: X = Br



4

a: R = Ac, X = Br
b: R = Ac, X = OTs
c: R = Bz, X = Br
d: R = H, X = OBz



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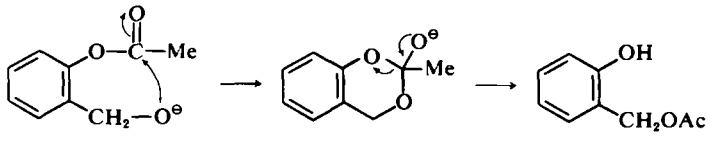

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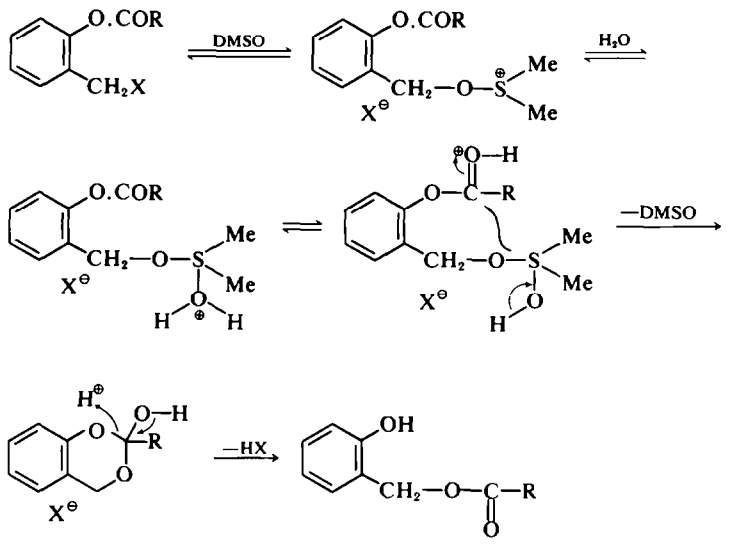


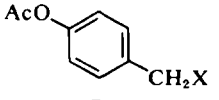
SCHEME 1

was recovered unchanged after seven days in DMSO: only when heated was 4-acetoxybenzyl alcohol **7b** formed to a small extent and most of the substrate was again recovered. The major product (9%) was 4-acetoxybenzaldehyde, the Kornblum-type reaction product. Thus, while the reaction is intramolecular, it is unlikely that a benzyl alcohol is an intermediate. We propose the mechanism outlined in Scheme 1 for the oxidative rearrangement. It involves the initial formation of benzyloxysulphonium salt (as shown by Torssell[8] for the reaction of benzyl bromides with anhydrous DMSO) followed, after reaction with water, by the formation of an ortho ester-type intermediate similar to that proposed by Wakselman[6] for the ester interchange rearrangement of *o*-acyloxybenzyl alcohols.

Turning to a study of phenacyl bromides, it was found by Kornblum and co-workers[9] that these compounds react with anhydrous DMSO, without a catalyst, to form phenyl glyoxals. Mayor and Hess[10] isolated phenyl glyoxalic acids also and Saikachi and Matsuo[11] found that thioformates (e.g. **16**) were formed to a minor extent. We now have observed that *o*-acyloxyphenacyl bromides react considerably faster in moist DMSO than the corresponding benzyl bromides and that a reaction leading to the formation of 2-hydroxycoumaran-3-ones **10** occurs to a similar extent as oxidative rearrangement. 2'-Acetoxy-2-bromoacetophenone **8a** yielded 2-acetoxy-2'-hydroxyacetophenone **9a** and 2-hydroxycoumaran-3-one **10a**. This coumaranone was also obtained from 2'-benzoyloxy-2-bromoacetophenone **8b**, together with 2-benzoyloxy-2'-hydroxyacetophenone **9b**.

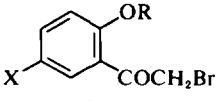
The formation of 2-hydroxycoumaran-3-one **10a** probably occurs (Scheme 2) *via* the acid-catalysed cyclization of the unknown 2-hydroxy-phenyl glyoxal **12**, the latter arising by de-esterification of the typical glyoxal product **11** of Kornblum oxidation of a phenacyl bromide. In accord with this, 2-bromo-2'-hydroxyacetophenone **8c** also yielded the 2-hydroxycoumaranone **10a**, together with 2,2'-dihydroxyacetophenone **13a**. Similarly, 2-bromo-5'-chloro-2'-hydroxyacetophenone **8d** yielded 5-chloro-2-hydroxycoumaran-3-one **10b** and 5'-chloro-2,2'-dihydroxyacetophenone **13b**.

The mechanism proposed for the oxidative rearrangement of *o*-acyloxyphenacyl bromides is outlined in Scheme 2. It is similar to that (Scheme 1) proposed for *o*-acyloxybenzyl bromides and tosylates except that it incorporates an alternative pathway, *via* a 2-hydroxyacetophenone **14**, for the rearrangement of the intermediate phenacyloxysul-



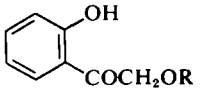
7

a: X = Br
b: X = OH



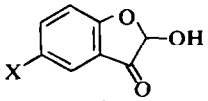
8

a: R = Ac, X = H
b: R = Bz, X = H
c: R = X = H
d: R = H, X = Cl



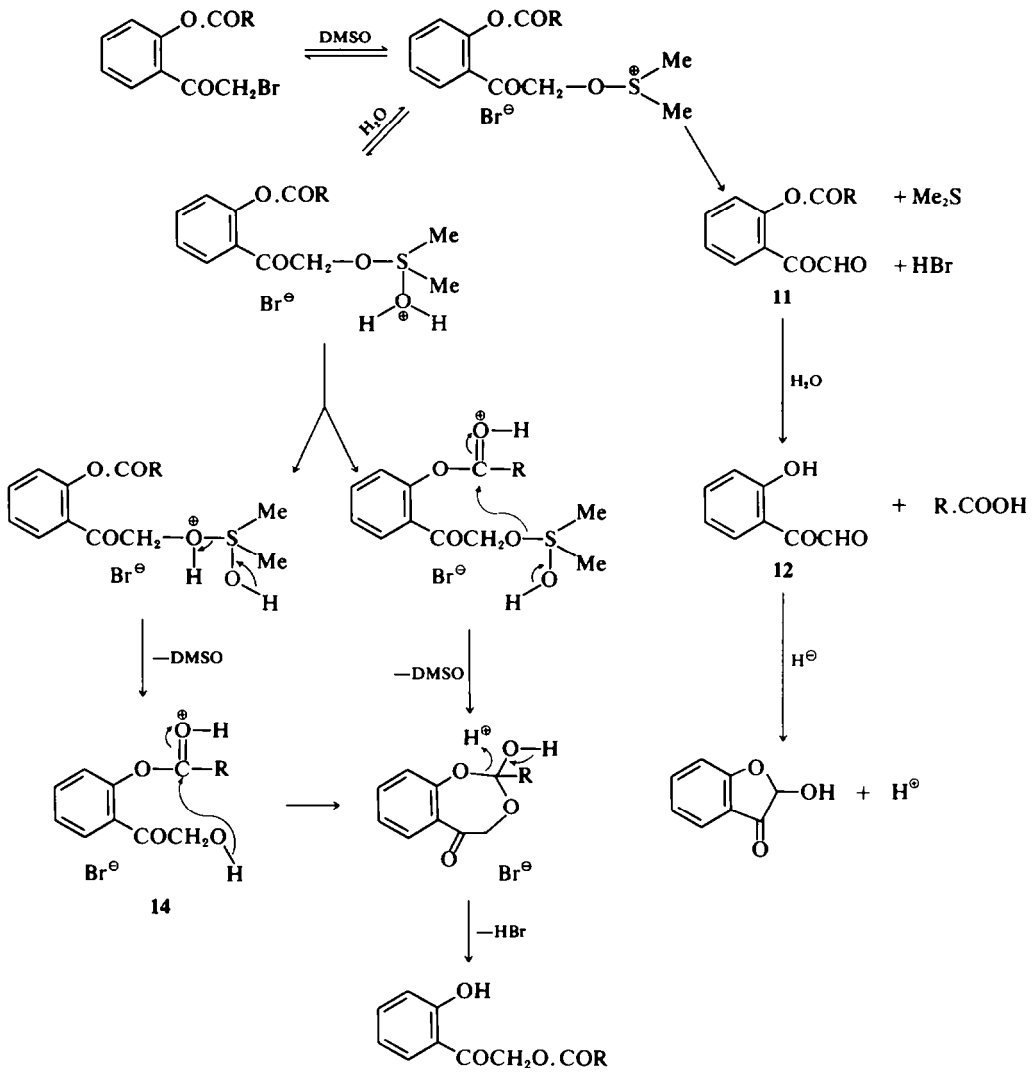
9

a: R = Ac
b: R = Bz



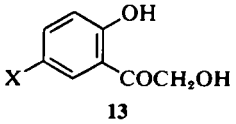
10

a: X = H
b: X = Cl



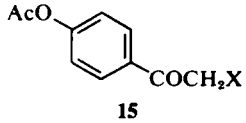
SCHEME 2

phonium salts. This was required by the ease with which the phenacyl bromides were hydrolysed (see above) to 2-hydroxyacetophenones in DMSO. 4'-Acetoxy-2-bromoacetophenone **15a** retained its ester group intact in DMSO and was converted into 4'-acetoxy-2-hydroxyacetophenone **15b**. A minor product from this reaction was methyl 4-acetoxybenzoyl thioformate **16**.



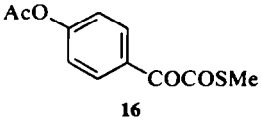
13

a: X = H
b: X = Cl



15

a: X = Br
b: X = OH



16

EXPERIMENTAL

NMR spectra were obtained at 60 MHz with a Perkin Elmer R12 spectrometer, in $CDCl_3$ with TMS as internal reference. M.ps were taken with a Kofler hot-stage apparatus.

Benzyl and phenacyl bromides and tosylates

N-Bromosuccinimide (2·4 g) and benzoyl peroxide (0·1 g) were added in four equal amounts, at 15 min intervals, to a refluxing solution of 2-acetoxy-5-bromotoluene[13] (3·0 g) in CCl_4 (30 ml). The cooled solution was filtered and solvent was removed under reduced pressure. The residual oil crystallised from light petroleum (b.p.

Table. Reactions of bromides and tosylates in dimethyl sulphoxide

Substrate	Amount (g)	Time (h)	Temp. (°C)	Product mixture	M.p. (°C) (solvent)[a]	Yield	Formula or	Found (%) Required (%)			NMR spectra[b,c] (τ values)
2-Acetoxybenzyl bromide[17] **2a**	1·0	72	20	2-Hydroxybenzyl acetate		c					
				5-Bromo-2-hydroxybenzyl acetate **3b**		c					
	0·25	2	85–90	5-Bromo-2-hydroxybenzyl acetate **3b**	98 (60–80)	0·125	16				OAc 7·86, CH_2 4·88, OH 2·19
2-Acetoxy-5-bromobenzyl bromide **4a**	0·5	72	20	Substrate		0·056					
				5-Bromo-2-hydroxybenzyl acetate **3b**	99–100 (60–80)	0·31	16				
4-Acetoxybenzyl bromide[17] **7a**	0·25	168	20	Substrate	54 (60–80)	0·21					OAc 7·88, CH_2 5·55
	1·0	18	60–65	Substrate	53–54	0·75					
				4-Acetoxybenzyl alcohol **7b**	oil	0·035	17				OAc 7·70, CH_2 5·38, OH 7·32
				4-Acetoxybenzaldehyde	oil	0·063					OAc 7·64, CHO 0·00
2-Benzoyloxy-5-bromobenzyl bromide **4c**	0·5	96	20	Substrate	82–83	0·20					
				5-Bromo-2-hydroxybenzyl benzoate **4d**	83–84 (60–80)	0·25	$C_{14}H_{11}BrO_3$	54·9 54·8	3·7 3·6	26·2 26·0	CH_2 4·62
2-Acetoxybenzyl tosylate **2b**	0·1	4	20	2-Hydroxybenzyl acetate **3a**	oil	0·048	6				OAc 7·88, CH_2 4·78, OH 2·30
2-Acetoxy-5-bromobenzyl tosylate **4b**	2·08	4	20	5-Bromo-2-hydroxybenzyl acetate **3b**	99–100 (60–80)	0·93	16				OAc 7·86, CH_2 4·88, OH 2·19
2-Acetoxybenzyl acetate[17] **2c**	1·0	1·5	120–125	Substrate		0·89					2-OAc 7·92, α-OAc 7·66, CH_2 4·88
2′-Acetoxy-2-bromoacetophenone[18] **8a**	0·3	28	20	*2-Acetoxy-2′-hydroxyacetophenone* **9a**	58–59 (60–80)	0·11	$C_{10}H_{10}O_4$	61·5 61·9	5·1 5·2		OAc 7·73, CH_2 4·59, OH −1·70
				2-Hydroxycoumaran-3-one[d] **10a**	104–105	0·10	23				CH 4·30, OH 4·75
2′-Benzoyloxy-2-bromoacetophenone **8b**	0·2	24	20	*2-Benzoyloxy-2′-hydroxyacetophenone* **9b**	104–105 (80–100)	0·03	$C_{15}H_{12}O_4$	70·6 70·3	4·5 4·7		CH_2 4·32, OH −1·73
				2-Hydroxycoumaran-3-one[d] **10a**	104–105 (80–100)	0·10					
2-Bromo-2′-hydroxyacetophenone[19] **8c**	0·36	16	20	2,2′-Dihydroxyacetophenone **13a**	64–65 (80–100)	0·08	23				CH_2 5·04, 2-OH 6·66, 2′-OH −1·54
				2-Hydroxycoumaran-3-one **10a**	102 (80–100)	0·09					
4′-Acetoxy-2-bromoacetophenone[20] **15a**	0·5	8	20	4′-Acetoxy-2-hydroxyacetophenone **15b**	92 (80–100)	0·15	21				OAc 7·65, CH_2 5·09, OH 5·80
				Methyl 4-acetoxybenzoyl thioformate **16**	55–57 (60–80)	0·05	$C_{11}H_{10}O_4S$[e]	55·4 55·5	4·4 4·2		OAc 7·63, SCH, 7·50
2-Bromo-5′-chloro-2′-hydroxyacetophenone **8d**	0·5	16	20	*5′-Chloro-2,2′-dihydroxyacetophenone* **13b**	98–99 (60–80)	0·21	$C_8H_7ClO_3$	51·6 51·5	4·2 3·8	18·9 19·0	CH_2 5·53, 2-OH 6·80, 2′-OH −1·45
				5-Chloro-2-hydroxycoumaran-3-one **10b**	115 $CHCl_3$	0·18	$C_8H_5ClO_3$	51·8 52·1	2·9 2·7	19·4 19·2	CH 4·31, OH 4·75

[a] Solvent of crystallisation; (60–80) is light petroleum (b.p. 60–80°) and (80–100) is light petroleum (b.p. 80–100°).
[b] Only non-aromatic signals are given; all hydroxyl signals disappeared on addition of D_2O.
[c] An inseparable mixture shown by NMR to contain these products only and in the ratio 23:11.
[d] UV spectrum: λ_{max}^{MeOH} 254 mμ and 329 mμ, log ε 3·99 and 3·56 respectively.
[e] Found: S, 13·2. Required S, 13·5%.

80–100°) in needles (3·0 g) of 2-acetoxy(1',5-dibromotoluene **4a**, m.p. 56°. Found: C, 35·2; H, 2·5; Br, 51·3; $C_9H_8Br_2O_2$ requires C, 35·1; H, 2·6; Br, 51·9%. NMR spectrum: OAc 7·71τ, CH_2 5·31τ.

The above conditions were used for the bromination of 2-benzoyloxy-5-bromotoluene[14] (1·0 g) in CCl_4 (15 ml) with *N*-bromosuccinimide (0·62 g) except that benzoyl peroxide had to be omitted because it rendered purification of the product difficult. 2-Benzoyloxy-1',5-dibromotoluene **4c**, m.p. 83–84°, crystallised (0·91 g) from light petroleum (b.p. 60–80°). Found: C, 45·5; H, 2·7; Br, 43·5; $C_{14}H_{10}Br_2O_2$ requires C, 45·4; H, 2·7; Br, 43·2%. NMR spectrum: CH_2 5·52τ.

Bromine (1·6 g) in acetic acid (20 ml) was added to a solution of 2'-benzoyloxyacetophenone[15] (2·4 g) in acetic acid (20 ml). After 3 h the mixture was diluted with water (300 ml) and the precipitated 2'-benzoyloxy-2-bromoacetophenone **8b**, m.p. 73–74°, crystallised (2·8 g) from light petroleum (b.p. 80–100°). Found: C, 56·5; H, 3·2; Br, 24·8; $C_{15}H_{11}BrO_3$ requires C, 56·4; H, 3·5; Br, 25·0%. NMR spectrum: CH_2 5·56τ.

A warm solution of 5'-chloro-2'-hydroxyacetophenone (5·1 g) in $CHCl_3$ (25 ml) was added to a suspension of cupric bromide (11·2 g) in refluxing ethyl acetate (25 ml). Refluxing was continued until the mixture was amber-coloured; it was then cooled and filtered and the solvent was removed under reduced pressure. The residual oil crystallised from light petroleum (b.p. 60–80°) in yellow crystals (5·5 g) of 2-bromo-5'-chloro-2'-hydroxyacetophenone **8d**, m.p. 64–65°. Found: C, 38·4; H, 2·7; Hal, 46·0; $C_8H_6BrClO_2$ requires C, 38·5; H, 2·4; Hal, 46·2%. NMR spectrum: CH_2 5·54τ, OH −1·72τ.

AgOTs (1·5 g) was added to a solution of 2-acetoxy-1'-bromotoluene (1·2 g) in MeCN (20 ml) and protected from light. After 16 h, the solution was filtered and the solvent removed by distillation under reduced pressure. The residual white solid was extracted with Et_2O. Evaporation of the Et_2O gave an oil which crystallised from EtOH, giving 2-acetoxy-1'-tosyloxytoluene **2b** as colourless crystals (2·4 g), m.p. 72–74°. NMR spectrum: OAc 7·71τ, $ArCH_3$ 7·53τ, CH_2 4·91τ. Both this and the following tosylate rapidly decomposed and were not microanalysed.

2-Acetoxy-1',5-dibromotoluene (1·54 g) reacted similarly with AgOTs (1·48 g) in MeCN (20 ml) to give 2-acetoxy-5-bromo-1'-tosyloxytoluene **4b** as colourless crystals (1·75 g), m.p. 100–101°, from EtOH. NMR spectrum: OAc 7·68τ, $ArCH_3$ 7·51τ, CH_2 4·93τ.

Reactions of bromides and tosylates in DMSO

The details of these reactions are given in the Table. The substrates were dissolved in approximately 20 times their weight of undried DMSO (additional H_2O was found to be unnecessary). The reactions were worked-up by dilution with saturated aq NaCl and extration with Et_2O. The extracts were washed with water and dried before the solvent was removed under reduced pressure. The residue was then fractionated by preparative layer chromatography on silica gel.

Hydrolysis of 2-benzoyloxy-2'-hydroxyacetophenone **9b**

Aq KOH (0·5 ml; 50%) was added to a solution of the benzoate (0·25 g) in ethanol (25 ml). The solution was refluxed for 3 4h, diluted with water (50 ml), neutralised with dil HCl, concentrated on a rotary evaporator under reduced pressure, and extracted with $CHCl_3$. The extract was dried and solvent removed. The residual oil crystallised from light petroleum (b.p. 60–80°) in colourless needles (0·108 g) of 2,2'-dihydroxyacetophenone **13a**, m.p. 63–64°.

Reduction of 2-acetoxybenzaldehyde **5**

Sodium borohydride (0·16 g) was added to a soln of the aldehyde (0·50 g) in EtOH (10 ml) and H_2O (5 ml). After 15 min the mixture was diluted with water (25 ml), concentrated on a rotary evaporator under reduced pressure, and extracted with $CHCl_3$. The extract was dried and solvent removed. The residual oil was fractionated by preparative layer chromatography on silica gel into 2-hydroxybenzaldehyde (0·102 g) and 2-hydroxybenzyl acetate (0·316 g). Both products were oils and were characterised by comparison of their spectra with samples otherwise obtained.

REFERENCES

[1] N. Kornblum, W. J. Jones and G. J. Anderson, *J. Am. Chem. Soc.* **81**, 4113 (1959)
[2] W. L. Meyer and R. G. Olsen, *Can. J. Chem.* **45**, 1459 (1967)
[3] H. R. Nace and J. J. Monagle, *J. Org. Chem.* **24**, 1792 (1959); B. H. Klanderman, *ibid.* **31**, 2618 (1966); G. Wolczunowicz, F. G. Cocu and T. Pasternak, *Helv. Chim. Acta* **53**, 2275 (1970)
[4] Preliminary note: J. A. Donnelly, P. A. Kerr and P. O'Boyle, *Chem. and Ind.* 93 (1973)
[5] I. M. Hunsberger and J. M. Tien, *Chem. Ind.* 88 (1959)
[6] M. Wakselman, *C. R. Acad. Sci. (C)* **262**, 770 (1966)
[7] B. Helferich and H. M. von Blumencron, *Ber. Dtsch. Chem. Ges.* **86**, 1058 (1953)
[8] K. Torssell, *Acta Chem. Scand.* **21**, 1 (1967)
[9] N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Levant and W. M. Weaver, *J. Am. Chem. Soc.* **79**, 6562 (1957)
[10] R. T. Mayor and H. J. Hess, *J. Org. Chem.* **23**, 1563 (1958)
[11] H. Saikachi and J. Matsuo, *Chem. Pharm. Bull. Japan* **17**, 1260 (1969)
[12] R. Ramage, *Tetrahedron* **27**, 1499 (1971)
[13] J. N. Ashley and R. D. MacDonald, *J. Chem. Soc.* 1668 (1957)
[14] L. C. Raiford and J. E. Milbery, *J. Am. Chem. Soc.* **56**, 2727 (1934)
[15] T. S. Wheeler, *Org. Synth.* **32**, 72 (1952)
[16] K. Auwers and G. Buttner, *Liebigs Ann.* **302**, 131 (1898)
[17] *cf* R. Grice and L. N. Owen, *J. Chem. Soc.* 1947 (1963)
[18] P. Friedlander and J. Neudorfer, *Ber. Dtsch. Chem. Ces.* **30**, 1077 (1897)
[19] L. C. King and G. K. Ostrum, *J. Org. Chem.* **29**, 3459 (1964)
[20] K. W. Rosenmund and K. Pfroepffer, *Ber. Dtsch. Chem. Ges.* **90**, 1922 (1957)
[21] A. Robertson and R. Robinson, *J. Chem. Soc.* 1460 (1928)
[22] *cf* C. Eneback and J. Gripenberg, *Acta Chem. Scand.* **11**, 866 (1957)
[23] R. Howe, B. S. Rao and H. Heyneker, *J. Chem. Soc. (C)* 2510 (1967)