Alkylation, Acylation, and Beckmann Rearrangement of Oximes in the Presence of an Oxidation–Reduction System

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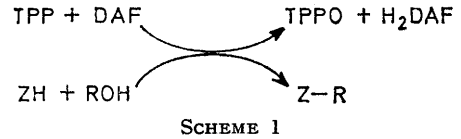
The system triphenylphosphine–diethyl azodiformate (TPP–DAF) can interact with oximes in the presence of either carboxylic acids or alcohols. Reactions of benzophenone oxime with a variety of aromatic carboxylic acids lead to *O*-acyl derivatives which undergo spontaneous Beckmann rearrangement. This modification of the Beckmann rearrangement takes place under very mild (0 °C), aprotic (tetrahydrofuran), and weakly acidic conditions, affording *NN*-diacyl aromatic amines as final products. The reaction of benzophenone oxime with alcohols in the presence of TPP–DAF gives *O*-alkyl ethers of the oxime. A mechanism is proposed.

THE system triphenylphosphine–diethyl azodiformate (TPP–DAF) can interact with an alcohol (ROH) and an acidic component (ZH) to yield an alkylation product (ZR) (Scheme 1).[1-3] This reaction can be regarded



SCHEME 1

either as an intermolecular dehydration, in which a molecule of water is abstracted from the alcohol and the acid, or as an oxidation–reduction in which triphenylphosphine is oxidized to triphenylphosphine oxide (TPPO) and the azo-compound is reduced to the appropriate hydrazo-derivative (H_2DAF). Acidic components that have been alkylated by this method include carboxylic acids,[4] phosphoric diesters,[5] cyclic imides,[6] phenols,[2] and diketones.[7]

Normal aromatic ketone oximes are weak acids (pK_a 11—12), and it might be expected that in the presence of an alcohol they would act as an acidic

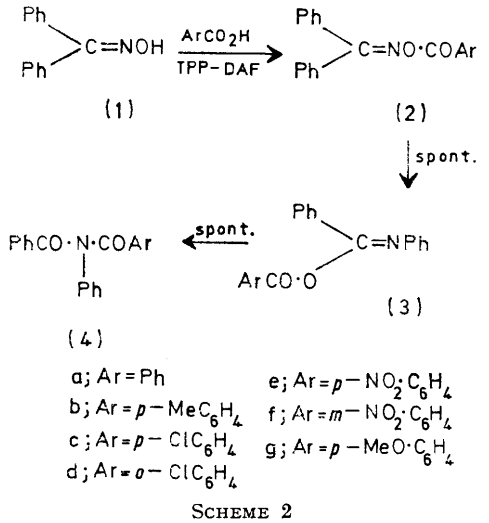
[1] O. Mitsunobu and M. Eguchi, *Bull. Chem. Soc. Japan*, 1971, **44**, 3427.
[2] S. Bittner and Y. Assaf, *Chem. and Ind.*, 1975, 281.
[3] S. Bittner, S. Grinberg, and Y. Assaf, Proceedings XXVth IUPAC Congress, Jerusalem, 1975, p. 85.
[4] O. Mitsunobu and M. Yamada, *Bull. Chem. Soc. Japan*, 1967, **40**, 2380.
[5] O. Mitsunobu, M. Yamada, and T. Mukaiyama, *Bull. Chem. Soc. Japan*, 1967, **40**, 935.
[6] O. Mitsunobu, M. Wada, and T. Sano, *J. Amer. Chem. Soc.*, 1972, **94**, 679.
[7] M. Wada and O. Mitsunobu, *Tetrahedron Letters*, 1972, 1279.

component (ZH), affording *O*-alkyloximes. On the other hand, in the presence of a stronger acid, the oxime might act as the hydroxylic component (ROH), yielding *O*-acyloximes. The present paper describes the behaviour of benzophenone oxime in such a system under various conditions.

Acylation and Beckmann Rearrangement.—When equimolar quantities of an aromatic carboxylic acid and benzophenone oxime (1) reacted in dry tetrahydrofuran, in the presence of TPP and DAF, the oxime was consumed within several hours (at 0 °C), as indicated by t.l.c., with concomitant formation of a new compound. This first product was transformed slowly (12—24 h) into a second, stable compound. The existence of a second reaction was supported by the i.r. spectra: initial samples showed ν_{CO} at 1 760—1 780 cm^{-1}, characteristic of *O*-acyloximes, shifting to 1 680—1 710 cm^{-1}, suggesting transformation into an amide. Work-up and purification gave high yields of *NN*-diacylaniline (4), identified by elemental analysis and i.r. and n.m.r. spectroscopy.

Efforts were made to isolate the intermediate; in one case, with *p*-toluic acid, the reaction was quenched after 2 h, when the conversion into (4) was still low. Rapid evaporation followed by silica gel chromatography gave benzophenone *O*-*p*-toluoyloxime (2b), identified on the basis of spectroscopic properties and elemental analysis.

The detection of the *O*-acyloxime (2) suggested that a Beckmann rearrangement was occurring. *O*-Acyloximes are known to undergo the Beckmann rearrangement readily and in the absence of catalyst.[8] The initial products are *O*-acyl imidic acid derivatives (3), which undergo further spontaneous rearrangement involving a 1,3 O-to-N shift of the acyl group. In the absence of water the final products are substituted diacylamines (4) (Scheme 2). No acylation reaction or rearrangement

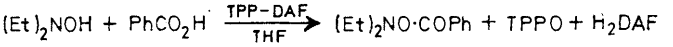


SCHEME 2

took place in the absence of the aromatic carboxylic acid: the benzophenone oxime was unchanged.

[8] P. A. S. Smith in ' Open Chain Nitrogen Compounds,' Benjamin, New York, 1966, p. 47.

In an analogous reaction *NN*-diethylhydroxylamine was transformed in the presence of TPP–DAF and benzoic acid into the *O*-benzoyl derivative. No rearrangement is possible here, and the reaction is terminated after the first step (Scheme 3).



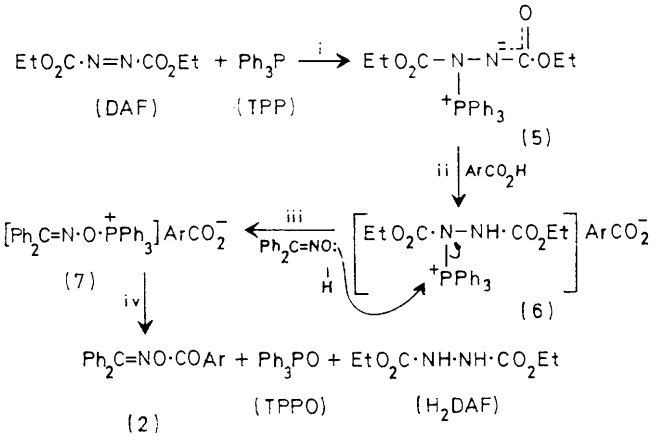
SCHEME 3

The i.r. and n.m.r. spectra of the diacylanilines (4a—g) are given in the Table.

I.r.[a] and n.m.r.[b] data for diacylanilines

Compd.	ν_{CO}	ν_{Ar}	δ_{ArH}	δ_{Me}
(4a)	1 695, 1 655	1 600	7.25—7.80 (m)	
(4b)	1 680	1 595	7.05—7.64 (m)	Me, 2.33 (s)
(4c)	1 680	1 590	7.20—7.75 (m)	
(4d)	1 685	1 590	7.15—7.71 (m)	
(4e)	1 710, 1 660	1 600	7.20—8.15 (m)	
(4f)	1 675	1 600	7.20—7.75 (m)	
(4g)	1 675	1 595	6.72—7.73 (m)	OMe, 3.80 (s)

[a] $\nu_{max.}$(Nujol)/cm^{-1}. [b] δ Values; solvent $CDCl_3$.



SCHEME 4

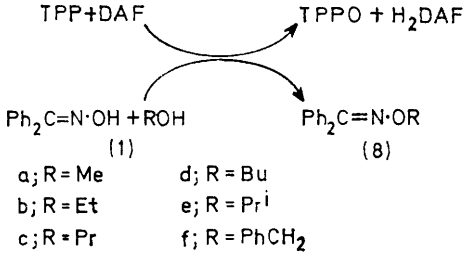
The proposed mechanism of this acylation reaction is outlined in Scheme 4. When TPP reacts with DAF it forms a labile adduct which is subjected to further reaction *in situ*. Owing to the high electrophilic activity of the nitrogen of DAF, it is believed [9] that the adduct is formed by nucleophilic attack on the nitrogen, forming a quasi-1,3-salt (5). This internal quaternary phosphonium salt is transformed in the presence of acid into a second, external phosphonium salt (6). The salt (6) is attacked by the oxime, with fission of the P–N bond, formation of the stronger P–O bond (7), and release of diethyl hydrazodiformate. Salts of type (7) are known to be powerful donors of the group attached to oxygen. The presence of an excellent leaving group (TPPO) is the driving force of the reaction. In our case, this leaving group is attached to the oxime nitrogen, and could be easily displaced by the nucleophilic carboxylate anion, forming the *O*-acyloxime (2). This

[9] E. Brunn and R. Huisgen, *Angew. Chem. Internat. Edn.*, 1969, 8, 513.

final reaction (step iv) provides a rare example of N–O fission in an oxime brought about by nucleophilic attack on the nitrogen. A number of examples of nucleophilic attack on nitrogen have been reported,[10-12] and in all these cases the nitrogen is hydroxylaminic in origin. The same is true in our case; however nucleophilic attack on an oxime nitrogen atom has not been reported hitherto.

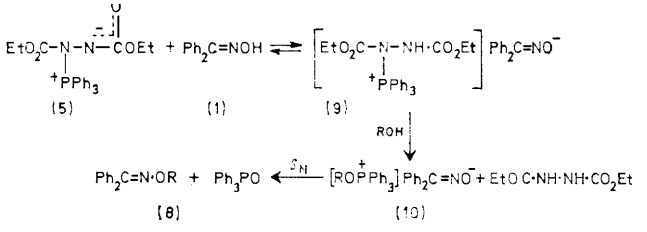
The foregoing general procedure involves a Beckmann rearrangement under very mild (0 °C), aprotic (tetrahydrofuran), and weakly acidic conditions. Almost all the usual procedures for this rearrangement involve the use of acidic reagents or of elevated temperatures, which induce isomerization of the oximes. In the present modification, the mild conditions preclude isomerization prior to rearrangement, and provide a convenient route to asymmetric diacylated aromatic amines.

Alkylation.—We next investigated the reaction of benzophenone oxime with alcohols in the presence of TPP–DAF. Oximes are poor nucleophiles, and react in the un-ionized state with only very active alkylating agents.[13] Under the present conditions, oximes underwent ready alkylation by alcohols. The reactions were performed at 0—5 °C in the alcohol as solvent with enough tetrahydrofuran added to dissolve the TPP. The *O*-alkyloximes (8) were obtained in 40—70% yield, and unlike the general alkylation reaction of oximes, no sign of nitrones was detected (Scheme 5).



SCHEME 5

The *O*-alkyl ethers may arise from the sequence illustrated in Scheme 6. By analogy with the mechan-



SCHEME 6

ism proposed for the acylation, the key intermediate is the zwitterionic salt (5) formed from DAF and TPP. This salt is in equilibrium with an external quaternary phosphonium salt (9) in which the oximate ion is the anion. The salt (9) is attacked by the alcohol in a process comprising fission of the N–P bond, release of diethyl hydrazodiformate, and formation of a new phosphonium salt (10). Within this salt, the nucleophilic oximate anion attacks, triphenylphosphine oxide is the leaving group, and benzophenone *O*-alkyloxime (8) is formed.

O-Alkyloximes are important precursors of aminooxy-compounds, and the present procedure provides a convenient synthesis of *O*-alkyloximes from alcohols. Preliminary studies have indicated that, under the conditions described, aromatic and aliphatic aldehyde oximes undergo fast dehydration yielding nitriles. The scope and mechanism of these reactions are under investigation.

EXPERIMENTAL

M.p.s were taken with an electrically heated silicone oil bath (Thomas–Hoover). I.r. spectra were recorded for Nujol mulls with a Perkin-Elmer 357 spectrometer (slow scan speed) and ^{1}H n.m.r. spectra for solutions in deuteriochloroform with 1% tetramethylsilane as internal standard (Varian EM 360 spectrometer).

All reactions were followed by t.l.c. on silica gel plates (Riedel-De-Haen AG DC karten SIF). Solvents were dried by standard techniques.

NN-*Dibenzoylaniline* (4a).—A solution of diethyl azodiformate (1.74 g, 10.0 mmol) in dry tetrahydrofuran (5 ml) was added dropwise to a stirred solution of triphenyl phosphine (1.96 g, 7.5 mmol), benzophenone oxime (0.98 g, 5.0 mmol), and benzoic acid (0.61 g, 5.0 mmol) in dry tetrahydrofuran at 0—4 °C, in a current of nitrogen, at such a rate as to prevent warming. The mixture was then warmed to 25 °C, stirred for 18 h, and concentrated under reduced pressure. The semicrystalline residue was redissolved in hot methanol (10 ml), and on cooling *NN*-dibenzoylaniline (1.3 g, 88%) was precipitated; m.p. 163° (from methanol) (lit.,[14] 161—162°) (Found: C, 79.3; H, 5.3; N, 5.05. Calc. for $C_{20}H_{15}NO_2$: C, 79.7; H, 5.0; N, 4.65%).

Similarly prepared from benzophenone oxime and other aromatic carboxylic acids in dry tetrahydrofuran were N-*benzoyl*-N-p-*nitrobenzoylaniline* (87%), m.p. 176—177° (Found: C, 69.2; H, 4.0; N, 8.2. $C_{20}H_{14}N_2O_4$ requires C, 69.4; H, 4.0; N, 8.1%); N-*benzoyl*-N-p-*toluoylaniline* (74%), m.p. 158—159° (Found: C, 80.2; H, 5.5; N, 4.5. $C_{21}H_{17}NO_2$ requires C, 80.0; H, 5.4; N, 4.4%); N-*benzoyl*-N-p-*chlorobenzoylaniline* (76%), m.p. 128—129° (from ethanol) (Found: C, 71.9; H, 4.2; N, 4.05. $C_{20}H_{14}ClNO_2$ requires C, 71.7; H, 4.2; N, 4.2%); N-*benzoyl*-N-o-*chlorobenzoylaniline* (79%), m.p. 126° (Found: C, 71.7; H, 4.2; Cl, 10.9; N, 4.1%); N-p-*anisoyl*-N-*benzoylaniline* (77%), m.p. 164—165° (Found: C, 75.9; H, 4.9; N, 4.0. $C_{21}H_{17}NO_3$ requires C, 76.1; H, 5.1; N, 4.2%); and N-*benzoyl*-N-m-*nitrobenzoylaniline* (92%), m.p. 132—133° (Found: C, 69.5; H, 3.9; N, 7.85. Calc. for $C_{20}H_{14}N_2O_4$: C, 69.4; H, 4.0; N, 8.1%).

O-*Benzoyl*-NN-*diethylhydroxylamine*.—A solution of diethyl azodiformate (2.96 g, 0.017 mol) in dry tetrahydro-

[10] L. A. Carpino, *J. Org. Chem.*, 1965, **30**, 321.
[11] T. Sheradsky, *Tetrahedron Letters*, 1968, 1909; T. Sheradsky and Z. Nir, *ibid.*, 1969, 77.
[12] F. Yamamoto and S. Oae, *Bull. Chem. Soc. Japan*, 1975, **48**, 77.
[13] P. A. S. Smith and J. E. Robertson, *J. Amer. Chem. Soc.*, 1962, **84**, 1197.
[14] A. Mumm, *Ber.*, 1910, **43**, 889.

furan (5 ml) was added dropwise to a stirred and cooled solution of triphenylphosphine (3.93 g, 0.015 mol), *NN*-diethylhydroxylamine (0.89 g, 0.01 mol), and benzoic acid (1.22 g, 0.01 mol) in dry tetrahydrofuran, under nitrogen. The mixture was then left at room temperature for 20 h. The solvent was removed under reduced pressure and the residue was digested with hexane to remove most of the triphenylphosphine oxide and diethyl hydrazodiformate. The soluble fraction was extracted twice with aqueous 5% sodium hydrogen carbonate and the extracts were dried and evaporated. The resulting oil (1.2 g) was purified by column chromatography [dry column of alumina (300 g; 80—200 mesh; type F-20)]; elution with chloroform–benzene (70 : 30) gave O-*benzoyl*-NN-*diethylhydroxylamine* (1.05 g, 54%) as an oil, $\nu_{max.}$ 1 750 cm^{-1} (C=O); δ 1.05 (6 H, t), 2.9 (4 H, q), and 7.4—7.9 (5 H, m).

Benzophenone O-p-*Toluoyloxime*.—A solution of diethyl azodiformate (1.74 g, 0.01 mol) in dry tetrahydrofuran (5 ml) was added dropwise to a stirred and cooled solution of triphenylphosphine (1.96 g, 0.007 5 mol), benzophenone oxime (0.98 g, 0.005 mol), and *p*-toluic acid (0.68 g, 0.005 mol), in dry tetrahydrofuran under nitrogen. After 2 h stirring at 0 °C the solvent was removed under reduced pressure and the residue was digested with hexane to remove the product from triphenylphosphine oxide, diethyl hydrazodiformate and some *N*-benzoyl-*N*-*p*-toluoylaniline. The hexane was evaporated off and the semicrystalline residue was purified by column chromatography (silica gel). Elution with benzene gave *benzophenone* O-p-*toluoyloxime* (0.64 g, 41%), m.p. 73—74° (Found: C, 80.1; H, 5.4; N, 4.25. $C_{21}H_{17}NO_2$ requires C, 80.0; H, 5.40; N, 4.4%), $\nu_{max.}$ 1 780 cm^{-1} (C=O).

Benzophenone O-*Methyloxime*.—A solution of diethyl azodiformate (3.48 g, 0.02 mol) in dry methanol (5 ml) was added dropwise to a stirred and cooled solution of triphenylphosphine (3.93 g, 0.015 mol) and benzophenone oxime (1.97 g, 0.01 mol) in dry methanol (10 ml) and tetrahydrofuran (3 ml; to dissolve the TPP). After 36 h at room temperature the solvents were removed under reduced pressure and the residue was digested several times with dry hexane. The combined hexane solutions were evaporated, and the residue was purified by column chromatography on silica gel (150 g; 100—200 mesh). Elution with hexane and then with hexane–benzene gave *benzophenone* O-*methyloxime* (1.18 g, 56%), m.p. 60° (Found: C, 79.6; H, 6.2; N, 6.6. $C_{14}H_{13}NO$ requires C, 79.6; H, 6.2; N, 6.6%), δ 3.9 (3 H, s) and 7.2—7.35 (10 H, m).

Similarly prepared from benzophenone oxime and alcohols were *benzophenone* O-*ethyloxime* (67%), an oil (Found: C, 80.0; H, 6.6; N, 6.5. $C_{15}H_{15}NO$ requires C, 80.0; H, 6.6; N, 6.2%), δ 1.3 (3 H, t), 4.22 (2 H, q), and 7.2—7.5 (10 H, m); *benzophenone* O-*n-propyloxime* (42%), an oil (Found: C, 80.2; H, 7.4; N, 5.7. $C_{16}H_{17}NO$ requires C, 80.3; H, 7.1; N, 5.8%), δ 0.9 (3 H, t), 1.62 (2 H, m), 4.15 (2 H, t), and 7.35 (10 H, m); *benzophenone* O-*isopropyloxime* (46%), an oil (Found: C, 80.4; H, 7.0; N, 6.1. $C_{16}H_{17}NO$ requires C, 80.3; H, 7.1; N, 5.8%), δ 1.1 (6 H, d), 4.15 (1 H, septet), and 7.0—7.35 (10 H, m); *benzophenone* O-*butyloxime* (62%) (Found: C, 80.3; H, 7.3; N, 5.5. $C_{17}H_{19}NO$ requires C, 80.6; H, 7.5; N, 5.5%), δ 0.9 (3 H, t), 1.2—1.8 (4 H, m), 4.2 (2 H, t), and 7.0—7.4 (10 H, m); and *benzophenone* O-*benzyloxime* (32%), m.p. 58° (Found: C, 83.1; H, 5.8; N, 4.8. $C_{20}H_{17}NO$ requires C, 83.6; H, 5.9; N, 4.8%), δ 5.2 (2 H, s) and 7.0—7.4 (15 H, m).

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