# Diazoketones from the Interaction of Diazoalkanes with Carboxylic Acid–Dicyclohexylcarbodi-imide Mixtures

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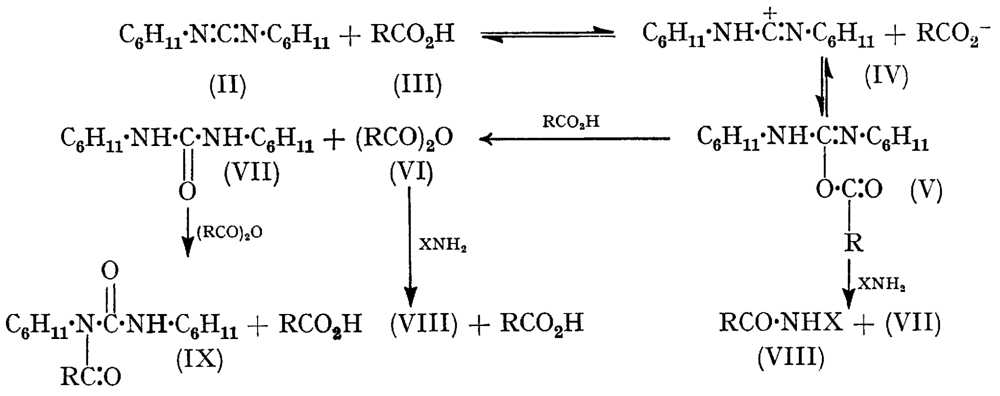
The addition of a mixture of a carboxylic acid (1 mol.) and dicyclohexylcarbodi-imide (1 mol.) in ether to diazomethane (1·25 mol.) or diazoethane (1·25 mol.) provides the corresponding diazo-ketone (*ca.* 0·5 mol.) through an acid anhydride intermediate. This procedure is useful for the preparation of diazo-ketones which cannot be prepared by conventional procedures from the acid chloride; *e.g.*, attempts to prepare 3-cyanopropionyl chloride have been unsuccessful but the addition of diazomethane to a mixture of 3-cyanopropionic acid and dicyclohexylcarbodi-imide gave 4-diazo-3-oxobutane-1-carbonitrile in *ca.* 30% yield.

THE acylation of diazoalkanes with acid chlorides,[1] or less commonly, acid anhydrides,[2] is a familiar procedure for the preparation of α-diazo-ketones (I; $R^2 = H$ or alkyl).

$$R^1COA + 2R^2CHN_2 \longrightarrow \underset{(I)}{R^1CO{\cdot}CR^2N_2} + R^2CH_2A + N_2$$

$$(A = Cl \text{ or } R^1CO_2)$$

In some instances, the requisite acid chloride or anhydride is not easy to prepare; we therefore considered the possibility of acylating diazomethane by a procedure analogous to that in which amines are converted into amides, by use of dicyclohexylcarbodi-imide (DCC)[3] (II). For this reaction, the amine ($XNH_2$) may be added in portions to a solution containing equimolecular proportions of a carboxylic acid and DCC. It has been suggested that the di-imide is first protonated to provide a cation (IV) which, on attack by the anion of the acid, yields the *O*-acyl derivatives of dicyclohexylisourea (V). The latter may then either acylate the amine directly or acylate a second molecule of the carboxylic acid to provide an acid anhydride (VI), which serves as the acylating agent. The molecule of free acid generated in the latter reaction may then be recycled so that ultimately virtually all the acid is converted into amide (VIII), the yield of which is the same whether the acylating agent be the adduct (V) or the anhydride (VI). In the acylation of diazoalkanes ($R^2CHN_2$), however, the nature of the acylating agent is important since, should it be the DCC–carboxylic acid adduct (V), the acid might be converted quantitatively into the diazo-ketone (I). If, however, the acid anhydride is formed, it will react with 2 mol. of diazoalkane to provide an equimolar mixture of diazo-ketone and methyl ester, and only 50% of the carboxylic acid will be converted into diazo-ketone.



We first used *p*-nitrobenzoic acid (III; $R = p\text{-}NO_2{\cdot}C_6H_4$), since the corresponding diazomethyl ketone α-diazo-*p*-nitroacetophenone, (I; $R^1 = NO_2{\cdot}C_6H_4$, $R^2 = H$) is relatively stable and well characterised. Addition of *p*-nitrobenzoic acid to a solution of DCC in ether gave a dense white precipitate after 2—3 min. After 30 min. the mixture, on treatment with diazomethane, gave α-diazo-*p*-nitroacetophenone in 50% yield. Some little time is apparently required for the acylating agent to form, since, if the carboxylic acid–DCC mixture is added to diazomethane after less than 30 min. ‘ incubation ’ methyl *p*-nitrobenzoate rather than diazo-ketone is formed. Indeed, the addition to diazomethane of a mixture of *p*-nitrobenzoic acid and DCC after less than 3 min. ‘ incubation ’ gave exclusively methyl *p*-nitrobenzoate, whereas extension of this time beyond 30 min. did not increase the yield of the diazo-ketone. Thus *ca.* 30 min. were apparently required for the formation of the acylating agent, which was apparently

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[1] W. Bradley and R. Robinson, *J. Chem. Soc.*, 1928, 1310, 1545, 2904; W. Bradley and J. K. Eaton, *ibid.*, 1937, 1914; B. Eistert, ‘ Newer Methods of Preparative Organic Chemistry,’ Interscience, New York, 1948, vol. 1, p. 513.

[2] W. Bradley and R. Robinson, *J. Amer. Chem. Soc.*, 1930, **52**, 1558; P. McC. Duggleby and G. Holt, *J. Chem. Soc.*, 1962, 3579.

[3] H. G. Khorana, *Chem. Rev.*, 1953, **53**, 145; E. Bricas, *Bull. Soc. chim. France*, 1961, 2001; M. Vilkas, *ibid.*, p. 2017.

the acid anhydride. Similar results were obtained for diazoethane. Attempts to reduce anhydride formation by adding the carboxylic acid in small portions to very dilute ethereal solutions of DCC were unsuccessful; the resulting mixtures gave α-diazo-*p*-nitroacetophenone in 50% yield. *m*-Nitro- and *p*-chlorobenzoic acids behaved similarly, providing the corresponding diazomethyl ketones (I; $R^1 = m\text{-}NO_2{\cdot}C_6H_4$, $R^2 = H$, and $R^1 = p\text{-}ClC_6H_4$, $R^2 = H$, respectively) (47 and 44% respectively). Further evidence that anhydride formation was involved was obtained by studying quantitatively the reaction between *p*-nitrobenzoic acid and DCC. Equimolecular proportions of the two were stirred in ether under nitrogen and after selected time intervals the unchanged DCC was estimated by Zetsche's method.[4] The results showed that 0·5 mol. of DCC was consumed in *ca.* 30 min., after which the DCC reacted more slowly (0·72 mol. after 15·5 hr). Similar results were obtained with phenylacetic acid, except that the reaction was slower. This rapid consumption of 0·5 mol. of DCC is consistent with the formation of acid anhydride [(II) + (III) $\longrightarrow$ (V) $\longrightarrow$ (VI)]. The subsequent slower reaction is probably a consequence of acylation of the dicyclohexylurea by the acid anhydride [(VII) $\longrightarrow$ (IX)]. This would liberate a molecule of carboxylic acid which would then be free to attack a molecule of DCC. Trifluoroacetic acid is known to give the corresponding *N*-trifluoroacetylurea (IX; $R = CF_3$) under similar conditions.[5]

With the restriction that only half of the carboxylic acid is converted into the corresponding diazo-ketone, a fairly general procedure has been developed for the preparation of these compounds by the DCC route (see Table).

| $R^1$ | $R^2$ | Yield of diazo-ketone (%) |
|---|---|---|
| $p\text{-}NO_2{\cdot}C_6H_4$ | H | 50 |
| $m\text{-}NO_2{\cdot}C_6H_4$ | H | 47 |
| $p\text{-}ClC_6H_4$ | H | 44 |
| $Ph{\cdot}CH_2$ | H | 11 |
| $p\text{-}NO_2{\cdot}C_6H_4$ | Me | 53 |
| $p\text{-}ClC_6H_4$ | Me | 44 |
| $N{\vdots}C{\cdot}CH_2{\cdot}CH_2$ | H | 30 |

4-Diazo-3-oxobutane-1-carbonitrile (I; $R^1 = N{\vdots}C{\cdot}CH_2{\cdot}CH_2$, $R^2 = H$) is of particular interest, since neither 3-cyanopropionyl chloride nor the corresponding anhydride appears to have been described and, in our hands, attempts to prepare them by conventional procedures were unsuccessful. Nonetheless, the addition of diazomethane to the mixture obtained by stirring α-cyanopropionic acid with DCC gave the hitherto unknown 4-diazo-3-oxobutane-1-carbonitrile in *ca.* 30% yield.

The yields of the diazo-ketones were confirmed by the weights of product obtained when weighed samples of crude diazo-compound were treated with toluene-*p*-sulphonic acid or were subjected to Wolff rearrangement. The values obtained were consistent with the volumes of nitrogen evolved during these reactions.

## EXPERIMENTAL

All the known diazo-ketones gave satisfactory i.r. data.

*Preparation of Diazo-ketones.—General procedure.* To a stirred solution of dicyclohexylcarbodi-imide (0·1 mole) in dry ether (200 ml.) was added the carboxylic acid (0·1 mole). After 4 hr. (initial reaction time), the mixture was added during 15 min. to an ice-cold solution of diazomethane or -ethane (0·15 mole) in ether (*ca.* 1 l.). The ice-cold solution was stirred until nitrogen was no longer evolved (1—3 hr.) and after removal of the slight excess of diazoalkane by evaporation under reduced pressure, the dicyclohexylurea (0·045—0·05 mole), m.p. and mixed m.p. 234°,[6] was filtered off and washed with a little cold ether. The combined filtrate and washings were evaporated to low bulk and the diazo-ketone was recrystallised. In a separate experiment, the crude diazo-ketone was treated with an excess of toluene-*p*-sulphonic acid in acetic anhydride by the procedure of Crowther and Holt,[7] and the yield of the diazo-compound was calculated from the weight of toluene-*p*-sulphonate obtained and from the volume of nitrogen liberated. The results obtained from the several acids used are as follows.

p-*Nitrobenzoic acid.* The acid with diazomethane gave α-diazo-*p*-nitroacetophenone (51%), m.p. 114—115° (from ethanol) (lit.,[8] 116—117°), and hence 4-nitrophenacyl toluene-*p*-sulphonate, m.p. 142° (from methanol) (lit.,[7] 142°). With an initial reaction time of <3 min. methyl *p*-nitrobenzoate (94%), m.p. 95—96°, was formed.[9] After initial reaction periods of 0·5, 2·0, and 4·5 hr., the yields of diazo-ketone were respectively 46, 50, and 56%. In the last case, gradual addition of the acid to the carbodi-imide solution and four-fold dilution of the reaction mixture did not raise the yield of the diazo-compound significantly.

*p*-Nitrobenzoic acid and diazoethane gave α-diazo-*p*-nitropropiophenone (53%), m.p. 105—107° [from light petroleum (b.p. 100—120°)] (lit.,[10] 109·5—110°), and hence 4-nitro-α-*p*-tolylsulphonyloxypropiophenone, m.p. 139—141° (from methanol).[7]

m-*Nitrobenzoic acid.* The acid and diazomethane gave α-diazo-*m*-nitroacetophenone (47%), m.p. 137—138° (decomp.) (from benzene), (lit.,[11a] 130·5—134°; lit.,[11b] 146—147°), and hence 3-nitrophenacyl toluene-*p*-sulphonate, m.p. 116—117° (from methanol) (lit.,[7] 118°).

p-*Chlorobenzoic acid.* The acid with diazomethane gave α-diazo-*p*-chloroacetophenone (44%), m.p. 109—113° [from light petroleum (b.p. 100—120°)] (lit.,[10] 112—114°), and hence *4-chlorophenacyl toluene-*p*-sulphonate*, m.p. 125·5—126° (from methanol) (Found: C, 55·7; H, 4·3; Cl, 11·1; S, 10·0. $C_{15}H_{13}ClO_4S$ requires C, 55·5; H, 4·0; Cl, 10·9; S, 9·9%). The diazo-ketone, on Wolff rearrangement (aniline–ethanol–silver nitrate) gave 4-chlorophenylacet-

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anilide (75%), m.p. 164—165° (from ethanol),[12] $\nu_{max.}$ 3225 (NH stretch), 1658s (CO), 1580s, 1332s, 1290m (amide III), 956s, 797s, 737s (CCl), and 686s cm.$^{-1}$. *p*-Chlorobenzoic acid with diazoethane gave α-diazo-*p*-chloropropiophenone (44%), m.p. 57—58° [from light petroleum (b.p. 100—120°)] (lit.,[10] 56—57·5°), and hence *4-chloro-α-*p*-tolylsulphonyloxypropiophenone*, m.p. 94—96° (from methanol) (Found: C, 56·7; H, 4·4. $C_{16}H_{15}ClO_4S$ requires C, 56·7; H, 4·5%), $\nu_{max.}$ 1725s (CO), 1613m, 1460s, 1365s and 1183s ($OSO_2$), 1022m, 929s, 817m, and 756m (CCl) cm.$^{-1}$. The diazo-ketone, on Wolff rearrangement[10] (benzyl alcohol–*NN*-diethylaniline) and subsequent hydrolysis of the benzyl ester gave α-(*p*-chlorophenyl)-propionic acid (39%), m.p. 56—57° [from light petroleum (b.p. 60—80°)] (lit.,[10] 57—58°), whereas with silver nitrate in ethanol containing aniline[13] it gave *β-anilino-*p*-chloropropiophenone* (96%), m.p. 122—123° (from ethanol) (Found: C, 69·3; H, 5·3; Cl, 13·4; N, 5·2. $C_{15}H_{14}ClNO$ requires C, 69·5; H, 5·4; Cl, 13·7; N, 5·4%), $\nu_{max.}$ 3382 (NH stretch), 2908m, 2847m, 1673 (CO), 1607m, 1585m, 1400s, 1152w, 869m, 793m, 747s (CCl), and 688s cm.$^{-1}$.

*Phenylacetic acid.* The acid and diazomethane gave benzyl diazomethyl ketone (11% based on yield of nitrogen evolved on Wolff rearrangement with silver benzoate in triethylamine[14]).

3-*Cyanopropionic acid.* The acid and diazomethane gave a mixture of methyl 3-cyanopropionate and 4-diazo-3-oxobutane-1-carbonitrile (30%), $\nu_{max.}$ 2240s (CN), 2110vs (diazo), and 1639s (ester CO) cm.$^{-1}$. This, with toluene-*p*-sulphonic acid in acetonitrile gave *3-oxo-4-*p*-tolylsulphonyloxybutane-1-carbonitrile*, m.p. 88—88·5° (from ethanol) (Found: C, 53·7; H, 4·9; N, 5·1; S, 11·9. $C_{12}H_{13}NO_4S$ requires C, 53·9; H, 4·9; N, 5·2; S, 12·0%), $\nu_{max.}$ 2222s (CN), 1712s (CO), 1353s, and 1179s ($OSO_2$) cm.$^{-1}$, and on Wolff rearrangement[13] (aniline–ethanol–silver nitrate) gave *4-cyanobutyranilide*, m.p. 79—80° (from benzene–light petroleum) (Found: C, 69·9; H, 6·4; N, 15·1. $C_{11}H_{12}N_2O$ requires C, 70·2; H, 6·4; N, 14·9%), $\nu_{max.}$ 3268s, 3205s, 3145s and 3077s (bonded NH), 2205m (CN), 1664s (CO), 1538s (amide II), and 720w broad (amide V) cm.$^{-1}$.

*Quantitative Investigation of the Carboxylic Acid–Dicyclohexylcarbodi-imide Interaction.*—Accurately weighed quantities of the carboxylic acid (*ca.* 0·8 g.) and DCC (*ca.* 1·0 g.) in dry ether (250 ml.) were stirred at 18—24°. The apparatus was purged with dry, carbon dioxide-free nitrogen before each determination. After the selected period of time an excess of oxalic acid (*ca.* 0·5 g.) in dry ether (50 ml.) was rapidly added. The carbon dioxide evolved was absorbed in an Anhydrone–soda asbestos train. After the initial vigorous reaction, the mixture was heated under reflux while a slow stream of dry nitrogen was passed through the apparatus for 1 hr. From the weight of carbon dioxide produced, the quantity of DCC remaining was calculated and hence the amount that had reacted with the carboxylic acid was determined. Duplicate runs on DCC alone showed that the estimation was accurate to better than ±1%. The results obtained with *p*-nitrobenzoic and phenylacetic acids are tabulated below.

| Reaction time (hr.) | DCC used (%) | |
|---|---|---|
| | *p*-Nitrobenzoic acid | Phenylacetic acid |
| 0·25 | 52·6 | 42·7 |
| 0·50 | 57·5<br>57·5 | 50·4<br>50·2 |
| 1·00 | 59·7<br>59·9 | 55·1 |
| 3·00 | | 59·2 |
| 5·00 | 69·9 | |
| 6·50 | | 64·6 |
| 9·50 | 69·4 | |
| 14·00 | | 65·7 |
| 15·50 | 71·8 | 72·5 |

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