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Reaction of Phenyl Azide with Amides of Malonic Acids and Phenylacetic Acid

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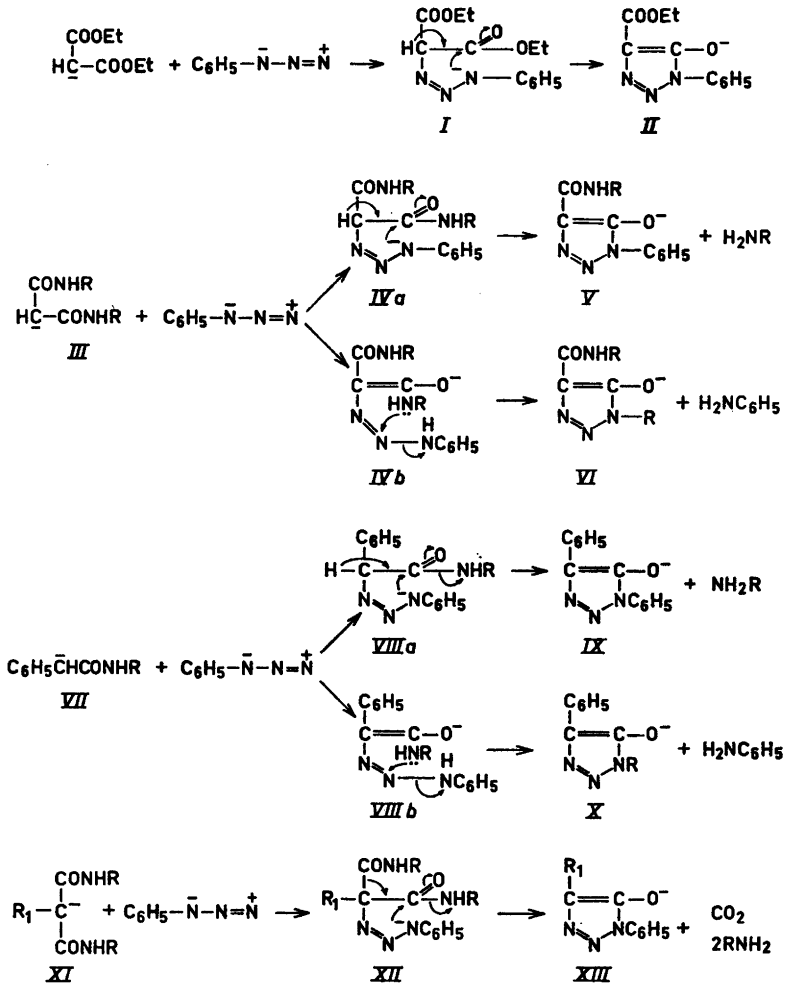
Reaction of phenyl azide with malonamide, phenylacetamide or their N-methyl derivatives gives mainly 5-hydroxy-1,2,3-triazoles, unsubstituted or substituted with a methyl group at position 1. When C-substituted malonamides or their N-methyl derivatives react with phenyl azide the main products are 1-phenyl-5-hydroxy-1,2,3-triazoles.

Dimroth has shown that reaction of diethyl malonate with phenyl azide, in the presence of sodium ethoxide, gives 1-phenyl-4-carbethoxy-5-hydroxy-1,2,3-triazole (II), probably with a triazene (I) as an intermediate.[1]

In analogy with this one might expect that malonamide (III, R = H), under similar conditions, would give 1-phenyl-4-carboxamido-5-hydroxy-1,2,3-triazole (V, R = H). Dimroth,[2] however, found that the reaction took a different course yielding 4-carboxamido-5-hydroxy-1,2,3-triazole (VI, R = H) and aniline, and he assumed that a triazene (IV, R = H) was an intermediate. We have repeated this reaction and obtained a 72 % yield of (VI). No trace of (V) was found.

The reaction of phenyl azide with a number of amides has now been studied. Thus, it was found that N,N′-dimethyl malonamide (III, R = CH_3) with phenyl azide gives 1-methyl-4-(N-methyl carboxamido)-5-hydroxy-1,2,3-triazole (VI, R = CH_3) in 67 % yield. Again no trace of the compound with structure (V, R = CH_3) could be found.

Phenylacetamide (VII, R = H) gave, when treated with phenyl azide and sodium ethoxide, a mixture of 1,4-diphenyl-5-hydroxy-1,2,3-triazole (IX) and 4-phenyl-5-hydroxy-1,2,3-triazole (X, R = H) with the latter predominating. Again a triazene (VIII, R = H) may be an intermediate in the reaction and if this triazene has the structure (VIIIa, R = H) the negatively charged nitrogen may attack the amide-carbon giving (IX) and ammonia. If, on the other hand, the triazene has the tautomeric structure (VIIIb, R = H) the amide-nitrogen can attack the middle nitrogen of the triazene with the formation of (X, R = H) and aniline, apparently the latter course of the reaction predominates in this case and is the only one in the case of malona-



mide or N,N′-dimethyl malonamide where the triazenes (IVa) or (IVb) could be formed. A similar reaction with N-methyl phenylacetamide (VII, R = CH_3) gave 1-methyl-4-phenyl-5-hydroxy-1,2,3-triazole (X, R = CH_3) as the only product. The introduction of a methyl group makes the amide-nitrogen more nucleophilic and it is, therefore, understandable that (VIIIb) becomes more reactive at the expense of (VIIIa) and that (X) is the only product.

Reaction of methylmalonamide (XI, R = H, R_1 = CH_3) with phenyl azide and sodium ethoxide gave 1-phenyl-4-methyl-5-hydroxy-1,2,3-triazole (XIII, R_1 = CH_3) as the sole product. The same triazole was obtained when N,N′-dimethyl methylmalonamide (XI, R = R_1 = CH_3) was used. In these two reactions the first step is probably the formation of a triazene (XII, R_1 = CH_3, R = H or CH_3) which, by attack of the negatively charged nitrogen

on the amide-carbon and simultaneous loss of the carboxamido group, yields (XIII). The triazene (XII) cannot have the tautomeric structure analogous to (IVb) or (VIIIb) and therefore (XIII) is the only product formed.

Phenylmalonamide (XI, R = H, $R_1 = C_6H_5$) gave 1,4-diphenyl-5-hydroxy-1,2,3-triazole (XIII, $R_1 = C_6H_5$) as the main product; a small amount of 4-phenyl-5-hydroxy-1,2,3-triazole (X, R = H) was also formed. Similarly N,N'-dimethyl phenylmalonamide (XI, $R = CH_3$, $R_1 = C_6H_5$) gave 1,4-diphenyl-5-hydroxy-1,2,3-triazole as the major product together with a small amount of 1-methyl-4-phenyl-5-hydroxy-1,2,3-triazole (X, $R = CH_3$). The formation of 4-phenyl-5-hydroxy-1,2,3-triazole (X, R = H) and its 1-methyl derivative (X, $R = CH_3$) in the latter two experiments may be explained by assuming that part of the triazene (XII) loses a carboxamido group prior to cyclisation. This would lead to the intermediate (VIIIa or b) and thus to (X).

EXPERIMENTAL

Melting points are uncorrected. The purity of all products was checked by thin layer chromatography on silica gel G using ethyl acetate-propanol-water (5-3-2) as solvent. The spots were detected by spraying with aqueous ferric chloride. Equivalent weights were determined by potentiometric titration with 0.1 N sodium hydroxide.

Reaction of amides with phenyl azide

Malonamide. The reaction was performed according to Dimroth[2] yielding 72 % of crude product. Recrystallization from water gave pure 4-carboxamido-5-hydroxy-1,2,3-triazole with m.p. 186–187° (decomp.) (Dimroth reports m.p. 196° (decomp.)). (Found: C 27.84; H 3.18; N 43.94. Calc. for $C_3H_4N_4O_2$: C 28.12; H 3.12; N 43.75 Equiv. wt.: Found 126; calc. 128).

N,N'-Dimethyl malonamide. To a solution of sodium (1.15 g) in ethanol (25 ml) was added N,N'-dimethyl malonamide[3] (6.51 g) and phenyl azide (5.95 g). The mixture was heated on a steam bath for 1 h during which time the product separated as a sodium salt. The sodium salt was washed with ethanol and dissolved in water (50 ml). Addition of hydrochloric acid yielded a precipitate of 6.6 g of crude product which on recrystallization from water (50 ml) gave 5.2 g (67 %) of 1-methyl-4-(N-methyl carboxamido)-5-hydroxy-1,2,3-triazole, m.p. 184–186°. Two additional recrystallizations caused no change in melting point. (Found: C 38.60; H 5.20; N 35.52. Calc. for $C_5H_8N_4O_2$: C 38.40; H 5.16; N 35.85. Equiv. wt.: Found 157; calc. 156).

Phenylacetamide. To a suspension of sodium ethoxide (1.77 g) in ethanol (15 ml) (when larger amounts of ethanol were used the yield of products was much lower) was added phenylacetamide (3.50 g) and phenyl azide (3.1 g) and the mixture was heated on a steam bath for 6 h. The ethanol was then removed *in vacuo*, water (40 ml) was added and the mixture was extracted with methylene chloride to remove unreacted material. The aqueous phase was acidified and cooled yielding 2.4 g of a product which, by thin layer chromatography, was shown to contain two compounds. The product was extracted with ether (5 × 15 ml), the ether was removed and the residue was recrystallized twice from benzene yielding 1.0 g (24 %) of 4-phenyl-5-hydroxy-1,2,3-triazole, m.p. 176–178°. After two additional recrystallizations the product was chromatographically pure, m.p. 178–180° (reported[4] m.p. 184°). (Found: C 59.60; H 4.30; N 26.10. Calc. for $C_8H_7N_3O$: C 59.62; H 4.38; N 26.07. Equiv. wt.: Found 158; calc. 161).

The ether-insoluble material was chromatographically pure; recrystallization from ethanol gave 0.50 g (8 %) of 1,4-diphenyl-5-hydroxy-1,2,3-triazole, m.p. 155–156°. Two additional recrystallizations led to an increase of the melting point to 157–158° (recorded[1] 150–151°). (Found: C 70.60; H 4.90; N 17.72. Calc. for $C_{14}H_{11}N_3O$: C 70.86; H 4.67; N 17.72). The melting point and the infrared spectrum of the product were identical with those of a sample prepared according to Dimroth.[1]

N-Methyl phenylacetamide. By the procedure described above 7.51 g of N-methyl phenylacetamide [5] gave 5.50 g of chromatographically pure product, m.p. 200°. Recrystallization from ethanol gave 3.1 g (55 %) of pure 1-methyl-4-phenyl-5-hydroxy-1,2,3-triazole, m.p. 203°. (Found: C 61.50; H 5.00; N 23.80. Calc. for $C_9H_9N_3O$: C 61.70; H 5.17; N 23.99. Equiv. wt.: Found 175; calc. 175).

Methylmalonamide. To a suspension of sodium ethoxide (10.2 g) in ethanol (20 ml) was added methylmalonamide [6] (5.81 g) and phenyl azide (5.95 g) and the mixture was heated on a steam bath for 6 h. The solvent was then removed *in vacuo*, water was added and the mixture was extracted with methylene chloride. Acidification of the aqueous phase caused precipitation of 5.6 g (64 %) of 1-phenyl-4-methyl-5-hydroxy-1,2,3-triazole with m.p. 148° (decomp.). Recrystallization from water caused no change in melting point. (Found: C 61.70; H 5.39; N 23.94. Calc. for $C_9H_9N_3O$: C 61.70; H 5.17; N 23.99. Equiv. wt.: Found 175; calc. 175). Dimroth [7] found m.p. 133—134° for this compound. However, a sample prepared according to Dimroth gave m.p. 147—148° (decomp.) and had the same infrared spectrum as the material prepared above.

N,N'-Dimethyl methylmalonamide. In the same way N,N'-dimethyl methylmalonamide [8] (7.21 g) gave 9.59 g of crude product which by recrystallization yielded 6.22 g (71 %) of 1-phenyl-4-methyl-5-hydroxy-1,2,3-triazole, m.p. 148°.

Phenylmalonamide. Analogously phenylmalonamide [9] (8.91 g) gave 3.67 g of a crude product which by thin layer chromatography was shown to contain two main components and traces of other compounds. Separation and purification as described under phenylacetamide gave 3.19 g (27 %) of 1,4-diphenyl-5-hydroxy-1,2,3-triazole and 0.26 g (6 %) of 4-phenyl-5-hydroxy-1,2,3-triazole.

N,N'-Dimethyl phenylmalonamide. From 10.31 g of N,N'-dimethyl phenylmalonamide 10.43 g of crude product was obtained. A thin layer chromatogram showed two spots. The product was recrystallized twice from a mixture of ethanol (*ca.* 400 ml) and water (*ca.* 800 ml) yielding 9.25 g (78 %) of chromatographically pure 1,4-diphenyl-5-hydroxy -1,2,3-triazole, m.p. 155°. Evaporation of the combined mother liquors followed by recrystallization from ethanol gave 0.77 g of product. Chromatography showed one spot corresponding to 1-methyl-4-phenyl-5-hydroxy-1,2,3-triazole; but the compound could not be isolated in a pure state.

N,N'-Dimethyl phenylmalonamide was prepared from dimethyl phenylmalonate and aqueous methylamine. The product was recrystallized from ethanol, m.p. 193°. (Found: C 64.10; H 7.05; N 13.78. Calc. for $C_{11}H_{14}N_2O$: C 64.04; H 6.84; N 13.58).

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