Reaction of Benzamide Oxime with DCC [1]

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Reaction of benzamide oxime (**1**) with *N,N'*-dicyclohexylcarbodiimide (**2**) afforded 5-cyclohexylamino-3-phenyl-1,2,4-oxadiazole (**3**), *N,N',N"*-tricyclohexylguanidine (**4**) and *N,N'*-dicyclohexyl urea (**5**). When acetone (**8a**) or ethyl acetoacetate (**8b**) was added as a trap, the yield of **3** increased slightly and *N*-(2-propylidene)cyclohexylamine (**9a**) or ethyl 3-cyclohexylamino-2-butenoate (**9b**) was obtained as well as products **4** and **5**. Acetylacetone (**8c**) and diacetyl (**8d**) were also used as the trap for the cyclohexylamino group. When *p*-toluenesulfonic acid was added as a catalyst, 1-cyclohexyl-5-cyclohexylamino-3-phenyl-1*H*-1,2,4-triazole (**11**) was obtained in low yield.

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N,N'-Dicyclohexylcarbodiimide (DCC) is a well known dehydrating agent in the synthetic field of peptides, nucleosides and heterocyclic compounds [2]. On the other hand, an interesting use of this reagent is for the component of heterocyclic compounds. For example, Bose and Garratt have reported the application of DCC to the synthesis of barbituric acid derivatives [3]. Kurzer and Wilkinson have also reported that the reaction of carbonylhydrazide derivatives with DCC afforded 4-cyclohexyl-3-cyclohexylamino-1,2,4-triazolin-5-one derivatives [4].

In a part of our synthetic studies using amide oxime derivatives, we have attempted the reaction of benzamide oxime with DCC and obtained 1,2,4-oxadiazole derivatives containing a cyclohexylamino group. We wish to describe the above reaction in more detail.

Treatment of benzamide oxime (**1**) with an equivalent mole of DCC (**2**) in chloroform solution at reflux afforded 5-cyclohexylamino-3-phenyl-1,2,4-oxadiazole (**3**) and *N,N',N"*-tricyclohexylguanidine (**4**) in 52 and 40% yields, respectively. A small amount of *N,N'*-dicyclohexylurea (**5**) was obtained as a by-product (5.4%). When two equivalent moles of **2** was used, the yield of **3** was slightly improved (54%) and most of the reagent added was recovered.

The structure of **3** was assigned from analytical data, infrared (ir) and nuclear magnetic resonance (nmr) spectral data and finally certificated by mixed melting point determination with an authentic sample which was derived from 5-hydroxy-3-phenyl-1,2,4-oxadiazole *via* chlorination of the hydroxyl group and subsequent treatment with cyclohexylamine following the methods described in the literatures [5]. Compounds **4** and **5** were also identified by comparison of their ir spectra with those of authentic specimen [6]. It was clear from the above results that a portion of **2** was consumed as a trap for the cyclohexylamino moiety leaving from an intermediate **A** (Chart 1).

A carboxylic acid could not be used as a trap in the above reaction, since it reacts with **1** in the presence of **2** to afford benzamide *O*-acyloxime derivative. That is, **1** was reacted with acetic acid and **2** giving benzamide *O*-acetoxime (**6**) and 5-methyl-3-phenyl-1,2,4-oxadiazole (**7**) in 86 and 7.7% yields respectively. Product **5** was also obtained in 95% yield.

We next attempted to use a carbonyl compound as a trap. That is to say, equivalent moles of **1** and **2** were reacted in acetone (**8a**) as a solvent and a trap to afford *N*-(2-propylidene)cyclohexylamine (**9a**) and product **3** in 32 and 54% yields as well as products **4** (7.0%) and **5** (8.6%). The structure of **9a** was identified by comparison of its ir spec-

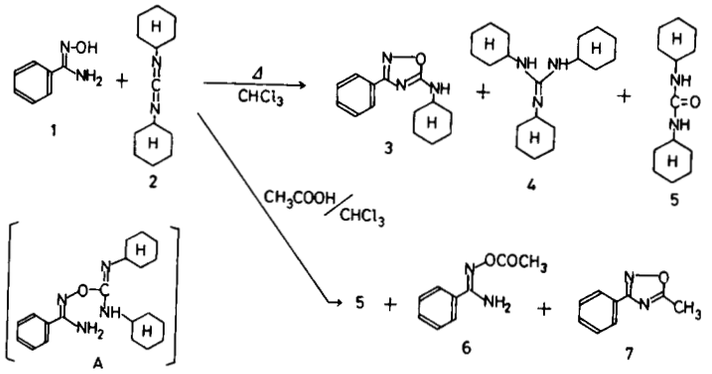

Chart 1

trum with that of an authentic sample [7].

When equivalent moles of **1**, **2** and ethyl acetoacetate (**8b**) were reacted in chloroform solution at reflux, products **3**, **4**, **5** and ethyl 3-cyclohexylamino-2-butenoate (**9b**) were obtained in 53, 12, 12, and 31% yields, respectively. A small amount of 3,5-diphenyl-1,2,4-oxadiazole (**10**) was also obtained (0.3%). The structure of **9b** was determined by comparison of its ir spectrum with that of an authentic sample which was derived from ethyl acetoacetate and cyclohexylamine followed by the method described in the literature [8]. From the above results, it was found that the addition of the trap **8a** and **8b** increased the yield of **3** to a small extent and at the same time obviously decreased the yield of **4**.

When acetylacetone (**8c**) was added as a trap, the yield of **3** could not be improved (41%), however, 4-cyclohexylamino-3-penten-2-one (**9c**) was obtained in 28% yield as well as products **4** (12%), **5** (5.0%), and **10** (0.1%). An appreciable amount of brown tarry substance was remained on the top of the flash column. Comparison of the ir spectrum of **9c** with that of an authentic sample furnished by condensation of **8c** with cyclohexylamine showed the identical spectral property [9].

When compound **1** was reacted with **2** in the presence of diacetyl (**8d**), a white precipitate appeared soon after stirring the reaction mixture at reflux (3-5 minutes) which was dissolved on further refluxing and the reaction mixture turned to reddish brown. After chromatographic workup on the above tarry reaction mixture, products **3**, **4**, **5** and 3-cyclohexylimino-2-butanone (**9d**) were obtained in 25, 15, 7.2 and 10% yields, respectively. A large amount of tarry substance was remained on the top of the flash column. The structure of **9d** was certificated by comparison of its ir spectrum with that of an authentic sample obtained from **8d** and cyclohexylamine [10].

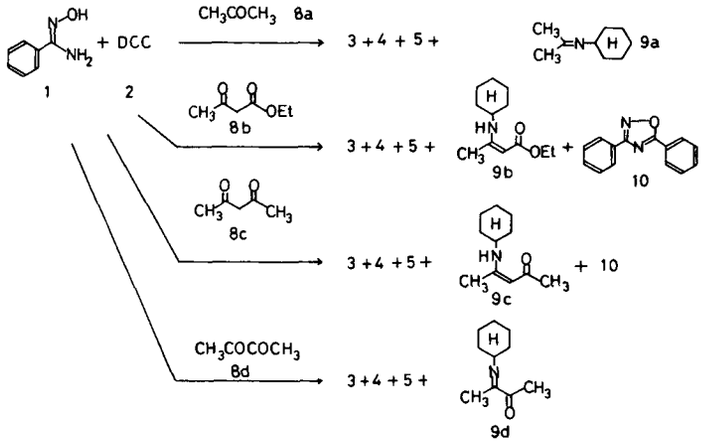

Chart 2

A possible mechanism for the formation of compound **3**, **4** and **9a-d** is shown in Chart 3. The first step of the reaction might well involve the formation of an adduct **A**, whether a trap **8** is added or not. When a trap is not present, cyclohexylamino moiety might be eliminated by pulling with the second DCC molecule to afford products **3** and **4** through path **a**. When a trap **8** is added to the reaction mixture, on the other hand, the elimination of the cyclohexylamino group might be performed preferentially by pulling with the trap molecule giving products **3** and **9a-d** following path **b**.

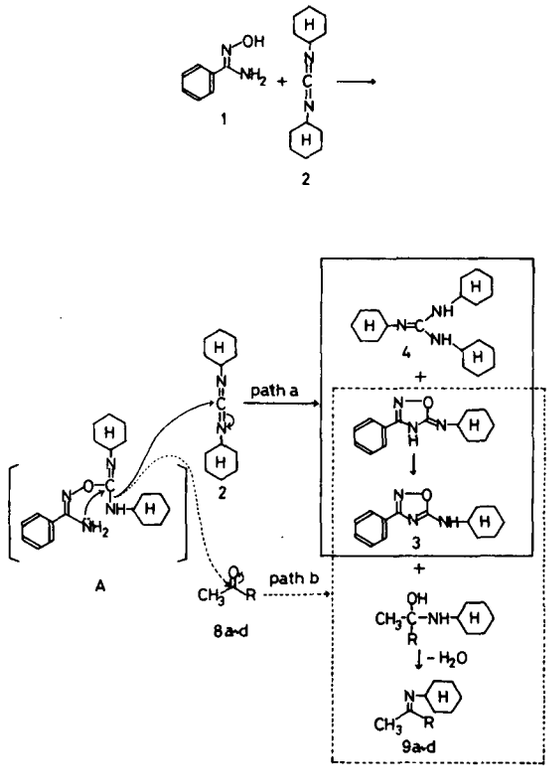

Chart 3

When *p*-toluenesulfonic acid was used as a catalyst, the reaction of **1** with **2** resulted in the formation of a large amount of brown tarry substance and the desired product **3** was obtained only in 7.9% yield by chromatographic workup. A small amount of colorless crystalline product **11** of mp 170° was obtained (1.3%) as well as products **5** (24%), **10** (3.1%), benzamide *O*-benzoxime (1.7%), benzamide (9.0%), and benzamide oxime *p*-toluenesulfonate (8.5%). However, compound **4** was not detected in the above reaction. The structure of **11** was reasonably assigned to be 1-cyclohexyl-5-cyclohexylamino-3-phenyl-1*H*-1,2,4-triazole from the analytical and spectral data.

Although several pathways could be taken into consideration for the formation of triazole derivative **11**, a likely mechanism is shown in Chart 4.

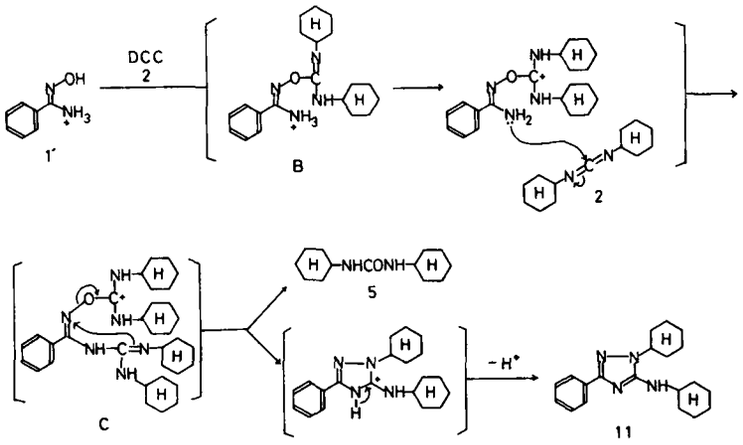

Chart 4

When *p*-toluenesulfonic acid is present as a catalyst, the first stage of the reaction might proceed with the formation of an adduct **B** from the protonated amide oximes **1'** and **2**. The adduct **B** might react with the second DCC molecule to form an adduct **C** which on elimination of dicyclohexylurea (**5**) and subsequent deprotonation gives triazole derivative **11**.

In conclusion, we found that the cyclization of amide oxime with C=N-cyclohexyl moiety of DCC gives 5-cyclohexylamino-1,2,4-oxadiazole ring and that an excess DCC or a carbonyl compound performs the role as a trap for the cyclohexylamino moiety of the intermediate.

EXPERIMENTAL

Melting points were determined on a Yanagimoto hot-stage melting point apparatus and are uncorrected. The ir spectra were recorded on a Hitachi 215 spectrophotometer. The nmr spectra were measured on a JEOL PS-100 and Varian EM-390 nmr spectrometer in deuteriochloroform with TMS as an internal standard. Mass spectra were obtained on a Hitachi M-80 spectrometer.

The flash chromatography was carried out on a Kimura Kagaku flash chromatography apparatus with Kieselgel 60 under the elution condition described in the literature [11]. The hplc was carried out using a Kusano Kagaku KP-6H hplc apparatus using a CIG column (silica gel, 50μ, 15ϕ×300 mm) and UVILOG 254 detector.

Reaction of Benzamide Oxime (**1**) with DCC (**2**).

A mixture of **1** (680 mg, 0.005 mole) and **2** (1.03 g, 0.005 mole) in 3.5 ml of dry chloroform was stirred for 4 hours at reflux. The precipitate which had formed was filtered and washed with chloroform (5 ml). The residue was subjected to hplc with *n*-hexane:ethyl acetate (2:1) as the eluent giving *N,N'*-dicyclohexylurea (**5**), mp 237° (25 mg) and *N,N',N"*-tricyclohexylguanidine (**4**), mp 200° (124 mg). The washing solution was concentrated to dryness and the residue was subjected to hplc with *n*-hexane:ethyl acetate (2:1) as the eluent affording 5-cyclohexylamino-3-phenyl-1,2,4-oxadiazole (**3**) (177 mg), **5** (35 mg) and **4** (185 mg).

The mother liquor was concentrated to dryness and the residue was subjected to flash chromatography with *n*-hexane:ethyl acetate (4:1) and (2:1) as the eluents giving an additional **3** (454 mg). The starting material **1** was also recovered in 28% (190 mg). The yields of products are shown in Table I.

Compound **3** had the following physical and spectral properties: mp 127°; ir (potassium bromide): 3300-3250 (NH), 2950 (CH), 1640 (C=N) cm^{-1}; nmr δ 1.20-2.10 (10H, m, cyclohexyl H), 3.70 (1H, m, CHN), 5.08 (1H, broad d, disappeared by deuterium substitution, NH), 7.47 (3H, m, benzene H), 8.00 (2H, m, benzene H) ppm; ms: m/e 243 (M^+).

Anal. Calcd. for $C_{14}H_{17}N_3O$: C, 69.11; H, 7.04; N, 17.27. Found: C, 69.03; H, 7.11; N, 17.35.

Table I

The Yields of Products **3**, **4**, **5**, **9a-d** and **10**

Run No.	Trap **8**	Yield of Product (%) **3**	**4**	**5**	**9**		**10**
1	—	52	40	5.4	—	—	—
2	**8a**	54	7.0	8.6	**9a**	32	—
3	**8b**	53	12	12	**9b**	31	0.3
4	**8c**	41	12	5.0	**9c**	28	0.1
5	**8d**	25	15	7.2	**9d**	10	—

Reaction of **1** with **2** in The Presence of Acetic Acid.

A mixture of **1** (136 mg, 1 mmole), **2** (206 mg, 1 mmole) and acetic acid (60 mg, 1 mmole) in 3.5 ml of dry chloroform was refluxed for 4 hours. After evaporation of the solvent, the residue was washed with ether (10 ml) and recrystallized from methanol giving **5** (211 mg, 95%).

The mother liquor and the washing solution were combined and concentrated to dryness. The residue was subjected to hplc with *n*-hexane:ethyl acetate (4:1) as the eluent giving benzamide *O*-acetoxime (**6**), mp 96° (125 mg, 86%) and 5-methyl-3-phenyl-1,2,4-oxadiazole (**7**), mp 42° (12 mg, 7.7%).

Reaction of **1** with **2** in Acetone (**8a**).

A mixture of **1** (136 mg, 1 mmole) and **2** (206 mg, 1 mmole) in 2 ml of acetone (**8a**) was refluxed for 5.5 hours. After evaporation of the solvent, the residue was subjected to hplc with *n*-hexane:ethyl acetate (6:1), (4:1) and (2:1) as the eluents giving *N*-(2-propylidene)cyclohexylamine (**9a**) (45 mg, 32%), **3** (131 mg, 54%), **5** (19 mg, 8.6%) and **4** (11 mg, 7.0%) in this order. The starting material **1** was recovered in 39% (53 mg).

Compound **9a** had the following physical and spectral properties: bp 180° [lit bp 180.6°, Ref 7]; ir (liquid film): 2950 (CH), 1675 (C=N) cm^{-1}; *nmr:* δ 1.20-1.99 (10H, *m, cyclohexyl* H), 1.83 (3H, s, CH_3), 1.98 (3H, s, CH_3), 3.20 (1H, m, CHN) ppm.

Reaction of **1** with **2** in The Presence of A Trap **8b-d**.

General Procedure.

A mixture of **1** (680 mg, 0.005 mole), **2** (1.03 g, 0.005 mole) and ethyl acetoacetate (**8a**), acetylacetone (**8b**) or diacetyl (**8d**) (0.005 mole) in 3.5 ml of dry chloroform was refluxed for 4 hours. After evaporation of the solvent, 5 ml of ethyl acetate was added to the residual oil and the mixture was standing overnight at room temperature. The precipitate which had formed was collected by filtration and washed with ethyl acetate (3 ml). The residue was subjected to hplc with *n*-hexane:ethyl acetate (4:1) and (2:1) as the eluents giving **5** and **4** in this order.

The mother liquor and the washing solution were combined and concentrated to dryness. The residue was subjected to flash chromatography using *n*-hexane:ethyl acetate (8:1), (6:1), (4:1) and (2:1) as the eluents affording five fractions. Each fraction was again subjected to hplc with the same eluent giving **3**, **4**, **5**, ethyl 3-cyclohexylamino-2-butenoate (**9b**), 4-cyclohexylamino-3-pentene-2-one (**9c**), or 3-cyclohexylimino-2-butanone (**9d**) and 3,5-diphenyl-1,2,4-oxadiazole (**10**), mp 106°. The yields of products are listed in Table I.

Compound **9b** had the following physical and spectral properties: bp 210°/3 mm Hg [lit bp 156-157°/0.12 mm Hg, ref 8]; ir (liquid film): 3260 (NH), 2950 (CH), 1690 (C=O), 1650 (C=N) cm^{-1}; nmr δ 1.20-2.00 (10H, m, cyclohexyl H), 1.21 (3H, t, J = 7 Hz, OCH_2CH_3), 1.92 (3H, s, CH_3-CH=), 3.35 (1H, m, CHN), 4.10 (2H, q, J = 7 Hz, OCH_2CH_3), 4.48 (1H, s, =CH-CO), 8.7 (1H, b, disappeared by deuterium substitution, NH) ppm.

Anal. Calcd. for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.18; H, 10.11; N, 6.45.

Compound **9c** had the following physical and spectral properties: bp 200°/4 mm Hg [lit bp 90-94°/0.04 mm Hg, ref 9]; ir (liquid film): 3280 (NH), 2930 (CH), 1690 (C=O), 1640 (C=N) cm^{-1}; nmr: δ 1.20-2.05 (10H, m, cyclohexyl H), 1.95 (3H, s, CH_3-C=), 2.01 (3H, s, CH_3-CO), 3.40 (1H, m, CHN), 4.95 (1H, s, CH-CO), 8.1 (1H, b, disappeared by deuterium substitution, NH) ppm.

Anal. Calcd. for $C_{11}H_{19}NO$: C, 72.88; H, 10.57; N, 7.73. Found: C, 72.76; H, 10.57; N, 7.59.

Compound **9d** had the following physical and spectral properties: bp 104°/15 mm Hg [lit bp 102-104°/15 mm Hg, ref 10] ir (liquid film): 2950 (CH), 1698 (C=O), 1645 (C=N) cm^{-1}; nmr: δ 1.20-2.00 (10H, m, cyclohexyl H), 1.93 (3H, s, CH_3-C=), 2.23 (3H, s, CH_3-CO), 3.46 (1H, m, CHN) ppm.

Anal. Calcd. for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.38. Found: C, 71.90; H, 10.22; N, 8.21.

Reaction of **1** and **2** in The Presence of *p*-Toluenesulfonic Acid.

A mixture of **1** (680 mg, 0.005 mole), **2** (1.03 g, 0.005 mole) and *p*-toluenesulfonic acid (950 mg, 0.005 mole) in 3.5 ml of dry chloroform was refluxed for 4 hours. After evaporation of the solvent, 5 ml of ethyl acetate was added to the residue and the mixture was standing overnight at room temperature. The precipitate which had formed was collected by filtration and washed with chloroform (10 ml). The residual solid was recrystallized from methanol giving **5** (156 mg).

The mother liquor and the washing solution were combined and concentrated to dryness. The residue was subjected to flash chromatography with *n*-hexane:ethyl acetate (8:1), (6:1), (4:1) and (2:1) as the eluents affording five fractions. Each fraction was again subjected to hplc with the same eluent to give **3** (96 mg, 7.9%), an additional **5** (112 mg, total yield was 24%), **10** (34 mg, 3.1%), 1-cyclohexyl-5-cyclohexylamino-3-phenyl-1*H*-1,2,4-triazole (**11**) (21 mg, 1.3%), benzamide, mp 130° (55 mg, 9.0%), benzamide *O*-benzoxime, mp 146° (20 mg, 1.7%) and benzamide oxime *p*-toluenesulfonate, mp 193° dec (113 mg, 8.5%), respectively.

Compound **11** has the following physical and spectral properties: mp 170°; ir (potassium bromide): 3250 (NH), 2860 (CH), 1580 (C=N) cm^{-1}; nmr: δ 1.20-2.20 (20H, m, cyclohexyl H), 3.45 (2H, m, CHN), 4.15 (1H, m, disappeared by deuterium substitution, NH), 7.4-7.5 (5H, broad s, benzene H) ppm.

Anal. Calcd. for $C_{20}H_{28}N_4$: C, 74.03; H, 8.70; N, 17.27. Found: C, 73.80; H, 8.67; N, 17.23.

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