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(*Journal of the Korean Chemical Society*)
Vol. 30, No. 2, 1986
Printed in the Republic of Korea

호모프탈산 무수물과 아조디카르복시산 에스테르 및 알킬리덴카르밤산 에스테르와의 고리화첨가반응

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(1985. 12. 2 접수)

Cycloaddition of Homophthalic Anhydrides to Azodicarboxylate and Alkylidenecarbamates

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(Received December 2, 1985)

요 약. 호모프탈산 무수물(**1** 또는 **2**)과 디에틸 아조디카르복시산 및 에틸 아릴메틸리덴카르밤산과의 고리화첨가반응을 검토하였다. 전자의 반응에서는 2,3-디에톡시카르보닐-2,3-디히드로-1-히드록시프탈라진들(**3** 및 **4**)이 생성되었으며, 후자의 반응에서는 3-아릴-4-카르복시-2-에톡시카르보닐-3,4-디히드로-1(2*H*)-이소퀴놀린온들(**5**~**10**)이 생성되었다.

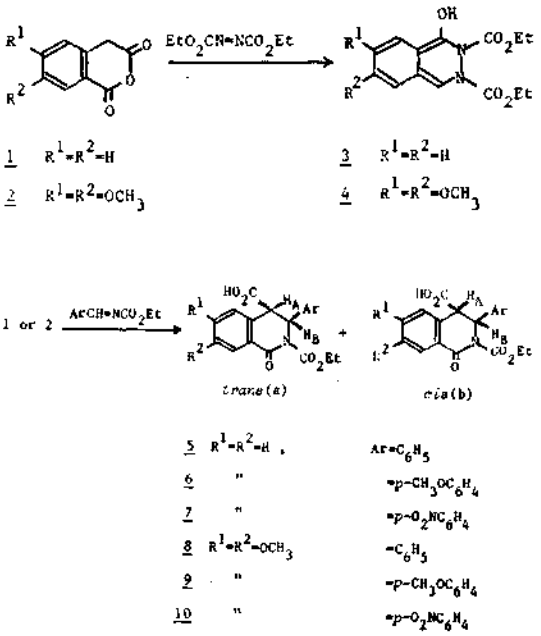
ABSTRACT. The cycloaddition between homophthalic anhydrides (**1** or **2**) and diethyl azodicarboxylate and ethyl arylmethyldenecarbamates was investigated. The former led to 2,3-diethoxycarbonyl-2,3-dihydro-1-hydroxyphthalazines (**3** and **4**), while the latter gave 3-aryl-4-carboxy-2-ethoxycarbonyl-3,4-dihydro-1(2*H*) isoquinolinones (**5**~**10**).

INTRODUCTION

Homophthalic anhydrides are known to react with C=O[1], C=N[2], C=C, and C≡C[3] dienophiles, and these cycloaddition reactions have been used for synthesis of some natural products. However, the C=N dienophiles reported so far in the reactions with homophthalic anhydrides are acyclic and cyclic imines. Furthermore, no cycloaddition reactions of homophthalic anhydrides to N=N dienophiles have been reported. We report here cycloaddition reactions of homophthalic anhydrides to an azodicarboxylate and to arylmethylidenecarbamates as a N=N and C=N dienophiles, respectively.

RESULTS AND DISCUSSIONS

The cycloaddition of homophthalic anhydride **1** to diethyl azodicarboxylate was attempted first under thermal conditions without success. We found that a base-induced cycloaddition reaction, developed recently by Tamura and his coworkers[3c] could be successfully applied to this cycloaddition. Thus, compound **1** was treated with an equivalent amount of sodium hydride in THF at 0°C to generate its anion, reacted with diethyl azodicarboxylate for 12 hr at room temperature, and then refluxed for 2 hr to give 2,3-diethoxycarbonyl-2,3-dihydro-1-hydroxyphthalazine (**3**) in 34% yleld. The analogous reaction



of 4, 5-dimethoxyhomophthalic anhydride (**2**) with diethyl azodicarboxylate led to the formation of 2, 3-diethoxycarbonyl-2, 3-dihydro-1-hydroxy-6, 7-dimethoxyphthalazine (**4**) in 28% yield. The ir spectra of **3** and **4** showed a hydroxy absorption band at 3000~3500 cm^{-1}. Their ^1H NMR and mass spectral data were consistent with the proposed structures.

The cycloadditions of **1** or **2** to arylmethylidenecarbamates were performed under thermal conditions. Arylmethylidenecarbamates were generated upon acid catalyzed decomposition of arylmethylidenebiscarbamates and reacted immediately with **1** or **2**. Thus, arylmethyledenebiscarbamates were treated with boron trifluoride etherate in benzene at refluxing temperature to generate the corresponding arylmethylidenecarbamates, which reacted with **1** or **2** under refluxing for 12~36 hr to give 3-aryl-4-carboxy-2-ethoxycarbonyl-3, 4-dihydro-1 (2*H*) -isoquinolinones (**5**~**10**) in 44~61 % yield. The cycloadducts **5**, **7** and **10** were all *trans* isomers, whereas **6**, **8** and **9** were mixtures of *trans* and *cis*, which were separated by column chromatography. The major diastereomers were *trans* ones which would be thermodynamically more stable. Spectral data of all cycloadducts were consistent with the proposed structures. The signals for proton H_A of *cis* diastereomers **6b**, **8b** and **9b** appeared at δ 4.65~4.75ppm in the ^1H NMR spectra, whereas *trans* isomers **5a**~**9a** showed its signals at δ 4.05~4.15ppm. The coupling constants J_{AB} for the *trans* isomers were observed as 1 Hz, whereas those for the *cis* isomers as 6 Hz. These observations are in close agreement with those reported for the related compounds[2a].

EXPERIMENTAL

Melting points were recorded on a Fisher-Johns melting point apparatus and are uncorrected. The ^1H NMR spectra were recorded on a Varian EM-360 Spectrometer and the data were given in ppm units downfield from TMS. The ir spectra were obtained with Perkin-Elmer 710 B Infrared Spectrophotometer. Mass spectra were measured with a Shimadzu LKB 900 Gas Chromatograph Mass Spectrometer. Analytical TLC was done on Merck Kiesel-gel 60 G (Art. 773). Column chromatography was performed with Merck Kiesel-gel 60 (Art. 7734). Benzene and THF were distilled from sodium and benzophenone, and stored over molecular sieve (4Å). Other chemicals and solvents were used without further purification. Homophthalic anydridide[4], 4, 5-dimethoxyhomophthalic anhydride[5], and arylmethylidenebiscarbamates[6] were prepared by literature methods. All reactions were performed under a nitrogen atomosphere.

2, 3-Diethoxycarbonyl-2, 3-dihydro-1-hydroxyphthalazine (3). A mixture of **1** (0.80 g, 5.0 mmol) and sodium hydride (60% in mineral

oil; 5.0 mmol) in anhydrous THF (30m*l*) was stirred at 0°C for 5 min, and was added with diethyl azodicarboxylate (0.90g, 5.0 mmol). The whole was stirred at 0°C for 30 min, allowed to warm to room temperature, stirred for 12 hr, and then refluxed for 2 hr. The reaction mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl (10m*l*), and added with 7% hydrochloric acid (7 m*l*). The resulting solution was extracted with methylene chloride (50m*l*). The organic layer was washed with 5% aqueous NaCl (20m*l*) and dried over Na_2SO_4. The solvent was removed and the residue was subjected to column chromatography. The product was eluted with chloroform–ethyl acetate (8 : 2) and recrystallized from diethyl ether–petroleum ether (9 : 1) to give colorless crystal (0.50 g, 34 %); mp 178°C; ^1H NMR ($CDCl_3$+DMSO-d_6) δ 0.95 (t, 6H, J=8Hz, $2CH_3$), 4.03 (q, 4H, J=8Hz, $2CH_2$), 7.8~8.1 (m, 6H, Ar, OH); IR (KBr) 3500~2900, 1800, 1300, 1080, 740 cm^{-1}; MS m/e (%) 292 (M^+, 1), 219 (37), 175 (51), 174 (100), 147 (20).

2, 3-Diethoxycarbonyl-2, 3-dihydro-1-hydroxy-6, 7-dimethoxyphthalazine (4). Compound **4** was prepared from **2** (1.1g, 5.0mmol) and diethyl azodicarboxylate (0.90g, 5.0mmol) by a similar method. The major product was collected by column chromatography using chloroform–diethyl ether (6 : 4) as an eluent and recrystallized from chloroform (0.50g, 28%); mp 205°C; ^1H NMR ($CDCl_3$) δ 1.20 (t, 3H, J=6Hz, CH_3), 1.23 (t, 3H, J=6.5Hz, CH_3), 3.92 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 4.15 (q, 2H, J=6.5Hz, CH_2), 4.22 (q, 2H, J=6 Hz, CH_2), 6.55 (s, 1H, Ar), 7.21 (s, 1H, Ar), 7.27 (s, 1H, Ar), 8.71 (s, 1H, OH); IR (neat) 3500~3200, 1750, 1500, 1250 cm^{-1}; MS m/e (%) 352 (M^+, 4), 280 (47), 279 (41), 208(75), 207 (100).

***trans*-4-Carboxy-2-ethoxycarbonyl-3, 4-dihydro-3-phenyl-1(2*H*)-isoquinolinone (5a).** A mixture of benzylidenebisurethane (1.3g, 5.0 mmol) and boron trifluoride etherate (0.2g) in benzene (20 m*l*) was refluxed for 20 min. Then, **1** (0.80 g, 5.0 mmol) was added in small portions over a period of 30 min. The mixture was refluxed for 12 hr. The resulting solution was cooled to room temperature and evaporated. After the ethyl carbamte in the reaction mixture was removed in vacuo (90°C, 1–2 torr), the residue was chromatographed on a silica gel column by eluting with chloroform–diethyl ether (8 : 2) to give **5a** (0.80g, 47%); an oil; ^1H NMR ($CDCl_3$) δ 1.24 (t, 3H, J=6.5Hz, CH_3), 4.16 (d, 1H, J_{AB}=1Hz, H_A), 4.26 (q, 2H, J=6.5Hz, CH_2), 6.22 (d, 1H, J_{AB}=1Hz, H_B), 7.10 (br, 5H, Ar), 7.3 (m, 2H, Ar), 8.1 (m, 2H, Ar), 10.45 (s, 1H, COOH); IR (neat) 3500~2800, 1740, 1620, 1220, 720cm^{-1}; MS m/e (%) 339 (M^+, 11), 295 (78), 251(44), 250 (29), 223 (100), 178 (50).

***trans*- and *cis*-4-Carboxy-2-ethoxycarbonyl 3, 4-dihydro-3-(*p*-methoxyphenyl)-1(2*H*)-isoquinolinone (6a and 6b).** Compounds **6a** and **6b** were prepared from **1** (0.80 g, 5.0 mmol) and *p*-methoxyphenylmethylidenebisurethane (1.5 g, 5.0 mmol) by a similar method. Chromatographic separation of the products on a sillica gel column by eluting with chloroform–diethyl ether (8 : 2) gave successively **6b** (0.14 g, 8%) and **6a** (0.81g, 43%); **6a**: an oil; ^1H NMR ($CDCl_3$) δ 1.25 (t, 3H, J=6.5Hz, CH_3), 3.68 (s, 3H, OCH_3), 4.10 (d, 1H, J_{AB}=1Hz, H_A), 4.29 (q, 2H, J=6.5Hz, CH_2), 6.20 (d, 1H, J_{AB}=1 Hz, H_B), 6.67 (d, 2H, J=8Hz, Ar), 7.03 (d, 2H, J=8Hz, Ar), 7.3(m, 2H, Ar), 8.1 (m, 2H, Ar), 10.1 (s, 1H, COOH); IR (neat) 3600~2800, 1750, 1620, 1240, 1000, 740 cm^{-1}; MS m/e (%) 369 (M^+, 5), 325 (37), 324 (37), 281 (38), 280 (73), 253 (59), 208

(32), 178 (11), 134 (100); **6b**: an oil; ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 3H, J=7.5Hz, CH_3), 3.73 (s, 3H, OCH_3), 4.33 (q, 2H, J=7.5Hz, CH_2), 4.75 (d, 1H, J_{AB}=6Hz, H_A), 6.05 (d, 1H, J_{AB}=6Hz, H_B), 6.66 (d, 2H, J=8.5Hz, Ar), 7.07 (d, 2H, J=8.5Hz, Ar), 7.5 (m, 2H, Ar), 8.3 (m, 2H, Ar), 9.11 (s, 1H, COOH); IR (neat), 3600~2800, 1740, 1620, 1240, 1000, 740 cm^{-1}.

***trans*-4-Carboxy-2-ethoxycarbonyl-3,4-dihydro-3(*p*-nitrophenyl)-1(2*H*)-isoquinolinone (7a)**. Compound **7a** was prepared from **1** (0.80 g, 5.0 mmol) and *p*-nitrophenylmethylidenebisurethane (1.6g, 5.0 mmol) by a similar method (refluxing time 18 hr). Chromatographic separation of the products on a silica gel column by eluting with chloroform-diethyl ether (8 : 2) gave **7a** (0.84 g, 44%); an oil; ^{1}H NMR ($CDCl_3$) δ 1.24 (t, 3H, J=7Hz, CH_3), 4.15 (d, 1H, J_{AB}=1Hz, H_A), 4.26 (q, 2H, J=7 Hz, CH_2), 6.25(d, 1H, J_{AB}=1Hz, H_B), 7.24 (d, 2H, J=8Hz, Ar), 7.3 (br, 2H, Ar), 7.95(d, 2H, J=8Hz, Ar), 8.15 (m, 2H, Ar), 8.85 (s, 1H, COOH); IR (neat) 3600~2800, 1740, 1620, 1520, 1240, 1000, 740 cm^{-1}; MS m/e (%) 384 (M^+, 4), 340 (32), 339 (38), 296 (36), 295 (60), 268 (72), 222 (40), 178 (41), 44 (100).

***trans*- and *cis*-4-Carboxy-2-ethoxycarbonyl-3,4-dihydro-6,7-dimethoxy-3-phenyl-1(2*H*)-isoquinolinone (8a and 8b)**. Compounds **8a** and **8b** were prepared from **2** (1.1g, 5.0mmol) and benzylidenebisurethane (1.3g, 5.0mmol) by a similar method (refluxing time, 24 hr). Chromatographic separation of the products on a silica gel column by eluting with chloroform-diethyl ether (9 : 1) gave successively **8b** (0.17 g, 8%) and **8a** (0.94g, 47%). Compound **8b** was recrystallized from methanol (mp 215°C); **8a**: an oil; ^{1}H NMR ($CDCl_3$) δ 1.29 (t, 3H, J=6.5 Hz, CH_3), 3.85 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.09 (d, 1H, J_{AB}=1 Hz, H_A), 4.18 (q, 2H, J=6.5Hz, CH_2), 6.23 (d, 1H, J_{AB}=1 Hz, H_B), 6.68 (s, 1H, Ar), 7.21 (s, 5H, Ar), 7.65 (s, 1H, Ar), 10.68 (s, 1H, COOH); IR (neat) 3600~2800, 1740, 1620, 1520, 1240, 100 cm^{-1}; MS m/e (%) 399 (M^+, 4), 355 (15), 310 (35), 309 (75), 282 (14), 178 (38), 28 (100); **8b**: ^{1}H NMR ($CDCl_3$) δ 1.29 (t, 3H, J=6.5Hz, CH_3), 3.89 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.28 (q, 2H, J=6.5 Hz, CH_2); 4.70 (d, 1H, J_{AB}=6 Hz, H_A), 6.07 (d, 1H, J_{AB}=6Hz, H_B), 6.65 (s, 1H, Ar), 7.11 (s, 5H, Ar), 7.71 (s, 1H, Ar), 8.5 (br, 1H, COOH); IR (KBr) 3600~2800, 1750, 1620, 1520, 1240, 1000, 750cm^{-1}.

***trans*- and *cis*-4-Carboxy-2-ethoxycarbonyl-3,4-dihydro-6,7-dimethoxy-3-(*p*-methoxyphenyl)-1(2*H*)-isoquinolinone (9a and 9b)**. Compounds **9a** and **9b** were prepared from **2** (1.1g, 5.0mmol) and *p*-methoxyphenylmethylidenebisurethane (1.5g, 5.0mmol) by a similar method (refluxing time, 36 hr). Chromatographic separation of the products on a silica gel column by eluting with chloroform-ethyl ether (8 : 2) gave successively **9b** (0.52g, 24%) and **9a** (0.78 g, 37%). Compound **9b** was recrystallized from ethyl acetate (mp 196°C); **9a**: an oil; ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H, J=6 Hz, CH_3), 3.73 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.03 (d, 1H, J_{AB}=1 Hz, H_A), 4.32 (q, 2H, J=6Hz, CH_2), 6.20 (d, 1H, J_{AB}=1 Hz, H_B), 6.71 (s, 1H, Ar), 6.76 (d, 2H, J=8Hz, Ar), 7.10 (d, 2H, J=8 Hz, Ar), 7.69 (s, 1H, Ar), 9.7 (br, 1H, COOH); IR (neat) 3600~2800, 1740, 1620, 1520, 1250, 1000cm^{-1}; MS m/e (%) 429 (M^+, 7), 385 (37), 384 (44), 340 (55), 339 (100), 312 (42), 208 (17), 207 (33), 178 (66); **9b**: ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, J=7 Hz, CH_3), 3.71 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.29 (q, 2H, J=7 Hz, CH_2),

4.67 (d, 1H, J_{AB}=6 Hz, H_A), 5.97 (d, 1H, J_{AB}=6 Hz, H_B), 6.69 (d, 2H, J=9 Hz, Ar), 7.09 (d, 2H, J=9Hz, Ar), 7.44 (s, 1H, Ar), 7.63 (s, 1H, Ar), 7.85 (s, 1H, COOH); IR (neat) 3600~3100, 1740, 1700, 1620, 1540, 1250, 1000 cm^{-1}.

***trans*-4-Carboxy-2-ethoxycarbonyl-3, 4-dihydro-6, 7-dimethoxy-3-(*p*-nitrophenyl)-1(2*H*)-isoquinolinone (10a)**. Compound **10a** was prepared from **2**(1.1g, 5.0mmol) and *p*-nitrophenylmethylidenebisurethane(1.6g, 5.0mmol) by a similar method(refluxing time, 20 hr). Chromatographic separation of the products on a silica gel column by eluting with chloroform-diethyl ether (8 : 2) gave **10a** (1.1 g, 50%); an oil; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, J=8 Hz, CH_3), 3.87 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.10 (d, 1H, J_{AB}=1 Hz, H_A), 4.35 (q, 2H, J=8 Hz, CH_2), 6.35 (d, 1H, J_{AB}=1 Hz, H_B), 6.71 (s, 1H, Ar), 7.35 (d, 2H, J=10Hz, Ar), 7.65 (s, 1H, Ar), 8.10 (d, 2H, J=10Hz, Ar), 9.70 (s, 1H, COOH); IR (neat) 3600~2800, 1740, 1620, 1520, 1250, 1000 cm^{-1}; MS m/e (%) 444 (M^+, 3), 400(54), 355 (33), 354 (69), 327 (34), 222 (40), 178 (82), 44 (100).

ACKNOWLEDGEMENT

The present studies were supported by the Basic Science Research Program, Ministry of Education, 1985.

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