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The Synthesis of 1,3,4-Benzotriazepin-5-one Derivatives from Isatoic Anhydrides

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The reaction of isatoic anhydrides (**1**) with 2-pyridylamidrazone afforded *N*-(2-aminophenyl)-2-pyridylamidrazones (**2**), which were then cyclized with acid to 1,3,4-benzotriazepin-5-one derivatives (**3**). The treatment of isatoic anhydride with 2-pyridylcarbonohydrazide gave 1-(2-aminophenyl)-2-(2-pyridinecarbonyl)-hydrazine (**5**), which was then dehydrated with polyphosphoric acid to 3-(2-aminophenyl)-5-(2-pyridyl)-1,3,4-oxadiazole (**6**), but not to **3**.

There have been several reports on the methods of synthesizing 1,3,4-benzotriazepine derivatives, and these compounds have been synthesized in recent years.

Bush[1] used 1-(2-aminobenzyl)-1-phenylhydrazine as the starting material for the 1,3,4-benzotriazepine system. On the other hand, 5-phenyl-1,3-dihydro-2*H*-1,3,4-benzotriazepin-2-ones[2-4] and 5-phenyl-2,3-dihydro-1*H*-1,3,4-benzotriazepines[5] were prepared from 2-aminobenzophenones. Readily-available isatoic anhydrides were also used as starting materials, and 2,3,4,5-tetrahydro-1*H*-1,3,4-benzotriazepin-2,5-diones,[6-7] -5-ones,[8] and 1,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones[9] were synthesized. 3,4-Dihydro-1*H*-1,3,4-benzotriazepin-2,5-diones[10] were prepared from *N*-alkyl-*N*-carboxyanthranilate.

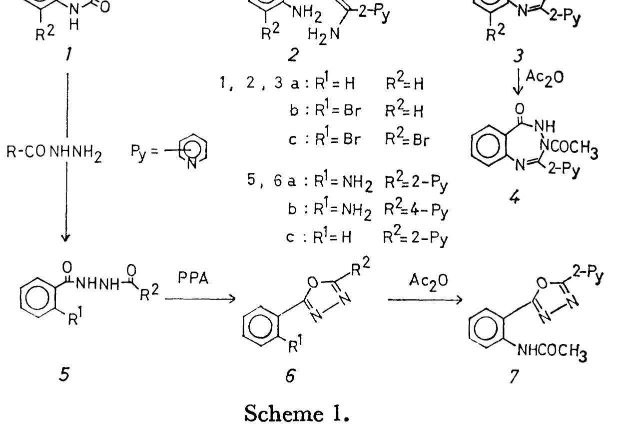
We have previously described the synthesis of 1,2,4-triazin-5-ones by the use of amidrazone.[11] In the present paper we wish to report a new method of synthesizing 1,3,4-benzotriazepin-5-ones by the reaction of isatoic anhydride with 2-pyridylamidrazone.

Results and Discussion

The reaction of isatoic anhydride with amines proceeds smoothly, with the evolution of carbon dioxide, to give *o*-aminobenzoylamide derivatives.[12] Thus, the reaction of readily-available 2-pyridylamidrazone[13] and isatoic anhydride (**1a**) in pyridine at room temperature gave *N*-(2-aminobenzoyl)-2-pyridylamidrazones (**2a**). From the substituted isatoic anhydrides (**1b**, **c**), *N*-(substituted-2-aminobenzoyl)-2-pyridylamidrazone (**2b**, **c**) were similarly obtained. The IR spectra of **2a**—**c** showed NH and CO stretching absorption bands at 3480—3160 and 1630—1618 cm^{-1} respectively. The deamination and cyclization of **2a** were attempted with acid catalysts or an acidic medium, and the treatment of **2a** with 0.05 M H_2SO_4–MeOH gave a yellow product (**3a**) in a moderate yield. **3a** was also formed on the refluxing of **2a** in acetic acid, but in a lower yield. The IR spectra of **3a** showed NH absorption bands at 3300 and 3190 cm^{-1} and CO and C=N absorption bands at 1675 and 1645 cm^{-1} respectively. The results of elemental analysis and the mass spectra supported the molecular formula corresponding to **3a**. The structure of **3a** of 2-(2-pyridyl)-3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-one was further confirmed by the formation of monoacetate (**4**), which was prepared on the heating of **3a** in acetic anhydride. **3b** was similarly obtained from **2b** in a good yield, but the structure of the product (**3c**) from **2c** was obscure from its spectral data.

Langis[9] reported the synthesis of analogous triazepine derivatives, **3**, from isatoic anhydride by a different route; the reaction of isatoic anhydride with acylhydrazines in EtOH afforded 1-aminobenzoyl-2-acylhydrazine (**5**), which were then dehydrated on heating with polyphosphoric acid to form **3**. Thus, we attempted to identify the structure of **3** by this route.

The treatment of **1a** with 2-pyridinecarbonohydrazide in EtOH gave 1-(2-aminobenzoyl)-2-(2-pyridyl)hydrazine (**5a**). The structure of **5a** was confirmed by analysis and by the spectral data. The dehydration of **5a** with polyphosphoric acid was examined under the condition described in the literature,[9] *i.e.*, at 150 °C for 1 hr. The IR and UV spectra of the product (**6a**) were analogous to those of the 4-pyridyl derivative (**6b**) prepared according to the reported procedure,[9] but were different from those of **3a**. However, the analytical data and the molecular weight determined by means of the mass spectrum of **6a** showed the same molecular formula as **3a**. The IR spectrum of **6a** showed two sharp NH absorption bands at 3440 and 3340 cm^{-1}. The absorption bands at 1640 and 1630 cm^{-1} were assigned to C=N stretching and NH deformation vibrations respectively. These data suggested that the structure of the product was not triazepine, **3a**, but 2-(2-aminophenyl)-5-(2-pyridyl)-1,3,4-oxadiazole. The NMR spectrum of **6a** displayed signals at δ 5.35 (NH_2) and at 6.6—8.9 (aromatic protons). Further confirmation of the structures of **3a** and **6a** could be



Scheme 1.

obtained by the correlation of the mass spectra; the spectrum of **3a** showed the main peaks at *m/e* 238 (M^+, 100%) and 208 (M^+—NH=NH, 59%), whereas in the case of **6a** the main peaks were at *m/e* 238 (M^+, 100%), 237 (M^+-1, 31%), and 120 (M^+—*o*-aminobenzonitrile, 34%).

The structure assignment of **6a** was further confirmed by a comparison of the analytical and spectral data of the monoacetate (**7**) with those of (**4**); elemental analysis and mass spectra gave an identical molecular formula. The IR spectrum of **4** showed two CO absorptions at 1685 and 1670 cm^{-1}, together with the NH absorption. On the other hand, **7** showed one CO absorption at 1690 cm^{-1}. **4** exhibited a mass spectrum characterized by a M^+ ion at *m/e* 280 (30%) in addition to significant peaks at *m/e* 237 (M^+—$COCH_3$, 93%) and 208 (M^+—$NH=NCOCH_3$, 100%). The high intense peaks of the spectrum of **7** at *m/e* 280 (100%), 237 (87%), and 120 (78%) were assigned to the M^+, M^+-COCH_3, and M^+—(2-CH_3CONH-C_6H_4-CN) ions respectively.

As the cyclization of diacyl hydrazines on treatment with dehydrating agents has already been reported,[14] we also attempted the cyclization of 1-benzoyl-2-(2-pyridyl)hydrazine (**5c**) as a model compound to 2-phenyl-5-(2-pyridyl)-1,3,4-oxadiazole (**6c**) under the same conditions as in the case of the reaction of **5a** to **6a**; we obtained **6c** in a moderate yield.

The structure of **3** was also supported by the hydrolysis of **3a** with hydrochloric acid to **5a** in a 45% yield.

From the above data, the compounds reported by Langies were not the triazepine derivatives **3** but 1,3,4-oxadiazoles, **6**; our results present a new synthetic route to 1,3,4-benzotriazepin-5-one derivatives.

Experimental

All the melting points are uncorrected. The IR, UV, and NMR spectra were measured with a JASCO Model IRA-2 spectrometer (KBr pellets), a Shimadzu Model MPS-50L spectrometer (in MeOH), and a Hitachi Model R-20 spectrometer respectively. A Shimadzu Model UM-3B apparatus was used for the elemental analysis.

N-*(2-Aminobenzoyl)-2-pyridylamidrazone (2a).* A mixture of 3.26 g (20 mmol) of **1a** and 3.26 g (24 mmol) of 2-pyridylamidrazone in 50 ml of pyridine was stirred at room temperature for 10 hr. The filtration and washing of the resulting precipitate with MeOH gave 4.26 g (84%) of **2a**. Recrystallization from pyridine afforded white needles; mp 223—225 °C. Found: C, 61.48; H, 5.10; N, 27.36%. Calcd for $C_{13}H_{13}N_5O$: C, 61.20; H, 5.14; N, 27.47%. IR: 3480—3200, 1660, 1630 cm^{-1}. UV λ_{max} nm (log ε): 217 (4.43), 250 (3.99), 317 (4.07), 336 (4.07).

N-*(2-Amino-5-bromobenzoyl)-2-pyridylamidrazone (2b).* A mixture of 2.42 g (10 mmol) of **1b** and 1.63 g (12 mmol) of 2-pyridylamidrazone in 20 ml of pyridine was refluxed for 1 hr. After cooling, the filtration and washing of the precipitate with MeOH gave 1.84 g (58%) of **2b**. Recrystallization from MeOH afforded yellow needles; mp 220—232 °C. Found: C, 46.60; H, 3.63; N, 20.49%. Calcd for $C_{13}H_{12}N_5OBr$: C, 46.72; H, 3.63; N, 20.96%. IR: 3440—3160, 1625 cm^{-1}. UV λ_{max} nm (log ε): 224 (4.61), 250 (4.43), 290 (4.14), 330 (3.95), 363 (4.04).

N-*(2-Amino-3,5-dibromobenzoyl)-2-pyridylamidrazone (2c).* **2c** was obtained in a 54% yield in the way which has been described for **2b**. Recrystallization from MeOH afforded yellow needles; mp 232—238 °C. Found: C, 37.39; H, 2.68%. Calcd for $C_{13}H_{11}N_5OBr_2$: C, 37.92; H, 3.01%. IR: 3438—3180, 1618 cm^{-1}. UV λ_{max} nm (log ε): 224 (4.41), 248 (4.21), 355 (4.05).

*2-(2-Pyridyl)-3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-one (3a).* A solution of 2.0 g (7.8 mmol) of **2a** in 50 ml of 0.05 M H_2SO_4–MeOH was refluxed for 3 hr. After the subsequent concentration and cooling of the solution, the precipitated crystals were filtered by suction and washed with water to remove the inorganic materials and then with MeOH to give 1.10 g (59%) of **3a**. Recrystallization from $CHCl_3$ afforded yellow needles; mp 247—248 °C. Found: C, 65.17; H, 4.36; H, 23.44%. Calcd for $C_{13}H_{10}N_4O$: C, 65.58; H, 4.24; N, 23.54%. IR: 3300, 3190, 3060, 1675, 1645 cm^{-1}. UV λ_{max} nm (log ε): 233 (4.33), 238 (4.31), 276 (4.17), 303 (3.96), 354 (2.95).

A solution of 200 mg of **2a** in 5.0 ml of acetic acid was refluxed for 3 hr. After cooling, the precipitated crystals were filtered by suction and washed with MeOH to give 59 mg (31%) of yellow products. Subsequent recrystallization from $CHCl_3$ afforded yellow needles, whose IR spectra and mp were identical with those of **3a**.

*7-Bromo-2-(2-pyridyl)-3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-one (3b).* **3b** was obtained in a 74% yield in the way described for **3a**. Recrystallization from MeOH afforded yellow needles; mp 249—250 °C. Found: C, 49.69; H, 2.81; N, 17.15%. Calcd for $C_{13}H_9N_4OBr$: C, 49.24; H, 2.86; N, 17.68%. IR: 3260, 3180, 3070, 3040, 2930, 1660, 1645 cm^{-1}. UV λ_{max} nm (log ε): 235 (4.40), 279 (4.26), 307 (3.95), 350 (2.79).

Monoacetate (4) of 3a. A solution of 300 mg of **3a** in 5.0 ml of acetic anhydride was refluxed for 2 hr. After cooling, the precipitated crystals were filtered by suction and washed with a small amount of ethyl acetate to give 145 mg (42%) of **4**. Subsequent recrystallization from benzene afforded yellow plates; mp 193—196 °C. Found: C, 64.17; H, 4.29%. Calcd for $C_{15}H_{12}N_4O_2$: C, 64.27; H, 4.32%. IR: 3270, 1685, 1670, 1650 cm^{-1}. NMR ($CDCl_3$): δ 2.48 (s, 3H), 6.9—8.8 (m, 8H), 9.30 (s, 1H).

1-(2-Aminobenzoyl)-2-(2-pyridyl)hydrazine (5a). A mixture of 2.4 g (15 mmol) of **1a** and 2.0 g (15 mmol) of picolinic acid hydrazide in 50 ml of EtOH was refluxed for 20 hr. After cooling, the precipitates were filtered by suction to give 2.2 g (71%) of **5a**. Recrystallization from MeOH afforded white prisms; mp 210—212 °C. Found: C, 60.93; H, 4.67%. Calcd for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72%. IR: 3500, 3380, 3300, 1685, 1675, 1644 cm^{-1}. UV λ_{max} nm (log ε): 250 (4.08), 338 (3.77).

Hydrolysis of 3a to 5a. A solution of 200 mg of **3a** in the mixing solvent of 5.0 ml of 1 M HCl and 5.0 ml of EtOH was refluxed for 2 hr. After cooling, the solution was neutralized with aqueous Na_2CO_3 and then allowed to stand to give precipitates. After the filtration of the precipitates, one recrystallization from MeOH afforded 97 mg (45%) of white crystals, whose mp and IR spectra were in accord with those of **5a**.

2-(2-Aminophenyl)-5-(2-pyridyl)-1,3,4-oxadiazole (6a). A mixture of 500 mg (2.0 mmol) of **5a** and 2.5 g of polyphosphoric acid was heated at 150 °C with gentle stirring for 1 hr. After cooling, the mixture was stirred into 50 ml of water, and the resulting precipitates were filtered off by suction. The filtrate was made alkaline with aqueous NaOH to give additional precipitates. The combined precipitates were washed with a small amount of MeOH to give 330 mg (61%) of **6a**. Recrystallization from MeOH afforded needles; mp 170—171 °C. Found: C, 65.60; H, 4.13%. Calcd for $C_{13}H_{10}N_4O$: C, 65.53; H, 4.23%. IR: 3440, 3340, 1640, 1630, 1615 cm^{-1}. UV λ_{max} nm (log ε): 220 (4.38), 249 (4.09), 285 (4.12), 358 (4.08).

2-(2-Aminophenyl)-5-(4-pyridyl)-1,3,4-oxadiazole (6b). **6b** was prepared according to the reported produre. Light yellow prisms; mp 191—192 °C (lit,9) 180—182 °C). IR: 3440, 3320, 3200, 1635, 1625 cm^{-1}. UV λ_{max} nm (log ε): 221 (4.46), 254 (4.19), 275 (4.24), 366 (4.10).

2-Phenyl-5-(2-pyridyl)-1,3,4-oxadiazole (6c). The crude product of **6c** was obtained in the way described for **6a**. The product was chromatographed on silica gel with the eluent of $CHCl_3$ to give 223 mg (48%) of pure **6c**. Recrystallization from MeOH afforded white needles; mp 131—132 °C. Found: C, 69.62; H, 3.95%. Calcd for $C_{13}H_9N_3O$: C, 69.94; H, 4.06%. IR: 3040, 1608, 1588, 1545 cm^{-1}. UV λ_{max} nm (log ε): 263 (4.19), 289 (4.38).

2-(2-Acetamidophenyl)-5-(2-pyridyl)-1,3,4-oxadiazole (7). A mixture of 250 mg (1.1 mmol) of **6a** and 5.0 ml of acetic anhydride was heated at 130 °C for 2 hr. The subsequent removal of the acetic anhydride *in vacuo* gave a solid residue, which was triturated with a small amount of water, filtered, and washed with MeOH to give 223 mg (72%) of **7**. Recrystallization from MeOH afforded white needles; mp 205—206 °C. Found: C, 64.12; H, 4.34%. Calcd for $C_{15}H_{12}N_4O_2$: C, 64.27; H, 4.32%. IR: 3260, 3200, 3060, 1690, 1616 cm^{-1}. UV λ_{max} nm (log ε): 225 (4.38), 242 (4.22), 287 (4.32), 294 (4.32), 315 (4.15). NMR ($CDCl_3$): δ 2.30 (s, 3H), 7.0—8.9 (m, 8H), 11.03 (s, 1H).

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