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Tricyclic Heteroaromatic Ring Systems IV.[1] Synthesis and Reactions of 4*H*-Pyrazolo[1,5—*a*]benzimidazole

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The 4*H*-Pyrazolo[1,5—*a*]benzimidazole ring system was prepared by an intramolecular *Ullmann* arylation of 4-substituted 1-(*o*-aminophenyl)pyrazole while other derivatives were obtained by functional group modifications. Some electrophilic substitutions (nitration, bromination) and alkylations were also carried out.

(Keywords: Alkylation; Bromination; Nitration; Ullmann arylation)

Tricyclische heteroaromatische Ringsysteme, 4. Mitt.: Synthese und Reaktionen von 4H-Pyrazolo[1,5—a]benzimidazolen

Das 4*H*-Pyrazolo[1,5—*a*]benzimidazol-System wurde mittels intramolekularer *Ullmann*-Arylierung von 4-substituierten 1-(*o*-Aminophenyl)pyrazolen hergestellt; weitere Derivate wurden dann durch Modifikation funktioneller Gruppen synthetisiert. Einige elektrophile Substitutionen (Nitrierung, Bromierung) und Alkylierungen wurden ebenfalls durchgeführt.

Introduction

A number of 4*H*-pyrazolo[1,5—*a*]benzimidazoles were prepared from appropriately substituted pyrazolones[3], aminopyrazolones[4], chloropyrazole[5], or benzimidazole[6]. Various derivatives of this system find use in color photography[3,4a–4d,7] or as dye intermediates[4e,8] while others are shown to be useful central nervous system stimulants of low toxicity[9]. The tautomerism of this system has also been studied in great detail by *Elguero* et al.[10].

We had earlier communicated[11] the synthesis of the basic ring system and now we wish to report the synthesis of some of its derivatives by intramolecular *Ullmann* arylation reaction[12] and some of their reactions.

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Results and Discussion

The starting materials for the *Ullmann* reaction [5-amino-1-(*o*-chlorophenyl)pyrazole-4-carbonitrile (**1**) and ethyl 5-amino-1-(*o*-chlorophenyl)pyrazole-4-carboxylate (**2**)] were obtained from the reaction of *o*-chlorophenylhydrazine with ethoxymethylenemalonitrile[13] and ethyl ethoxymethylenecyanoacetate[14] respectively. When **1** and **2** were heated with copper(II) oxide in *N*,*N*-dimethylformamide in the presence of anhydrous potassium carbonate the 3-carbonitrile (**3**) and 3-ester(**4**) derivatives of the parent ring system were formed in yields of 15% and 42% respectively. The structures of **3** and **4** were confirmed by the appearance of an NH absorption peak at 3 250 cm^{-1} in their infrared (IR) spectra. The proton magnetic resonance spectra (PMR) of **3** and **4** were also consistent with the structure. The PMR spectrum of **4** displayed a broad signal for the NH proton at δ 10.00. The mass spectra of the two compounds gave molecular ion peaks at *m*/e 182 (**3**) and 229 (**4**).

After the ring closures the cyano and carbethoxy groups were transformed into other derivatives. Thus the treatment of **3** with sodium azide gave the corresponding 3-(tetrazol-5′-yl)-4*H*-pyrazolo[1,5—*a*]benzimidazole (**5**) in 38% yield while hydrolysis with sulfuric acid gave 18% yield of the corresponding amide (**6**). The basic hydrolysis of **4** led to 71% yield of 4*H*-pyrazolo[1,5—*a*]benzimidazole-3-carboxylic acid (**7**). When **7** was heated above its melting point or *in vacuo*, it smoothly decarboxylated to give the parent ring system **8**.

To test the reactivity of this system we also carried out some reactions. The bromination of **8** gave a 3-bromo derivative (**9**) in 80% yield. The structure of **9** was confirmed by the disappearance of the doublet in **8** at δ 5.72 of the 3 proton of the system in its PMR spectrum. The doublet due to the 2 proton of the parent system had collapsed to a singlet at δ 7.80. There was, however, no change in the signals due to other protons. When the nitration of **8** was carried out with mixed acids at 60–65°, a 27% yield of a trinitrated product (**10**) was obtained. This product was characterized by its elemental analysis, infrared spectrum (νNO_2, 1 540 and 1 350 cm^{-1}), mass spectrum [*m*/e 292 (M^+)] and the PMR spectrum. The PMR spectrum in *HMPA* of **10** displayed a singlet at δ 8.40 for the proton at 2 position while two doublets with a coupling constant of 2.50 Hz at δ 8.68 and 8.93 are assigned to the protons at 6 and 8 position respectively. With a view to affect nitration in the phenyl ring, **4** was subjected to nitration under similar conditions but again **10** was the only product isolated from the reaction mixture, the carbethoxy group undergoing hydrolysis and decarboxylation under the reaction conditions. An attempt to nitrate selectively in the

pyrazole ring[15] **8** was nitrated with acetyl nitrate but the product isolated was the *N*-acyl compound (**11**), which was also obtained in the acylation of **8** with acetic anhydride. These electrophilic substitutions are further being investigated. Alkylation of **4** and **8** with ethyl iodide gave the corresponding *N*-ethyl derivatives **12** and **13** in 39 and 47% yields respectively. *Lazaró* and *Elguero*[10] have recently established that acylation and alkylation under the conditions used by us give the 4-acyl and alkyl products.

The various reactions are outlined in Scheme 1.

Scheme 1

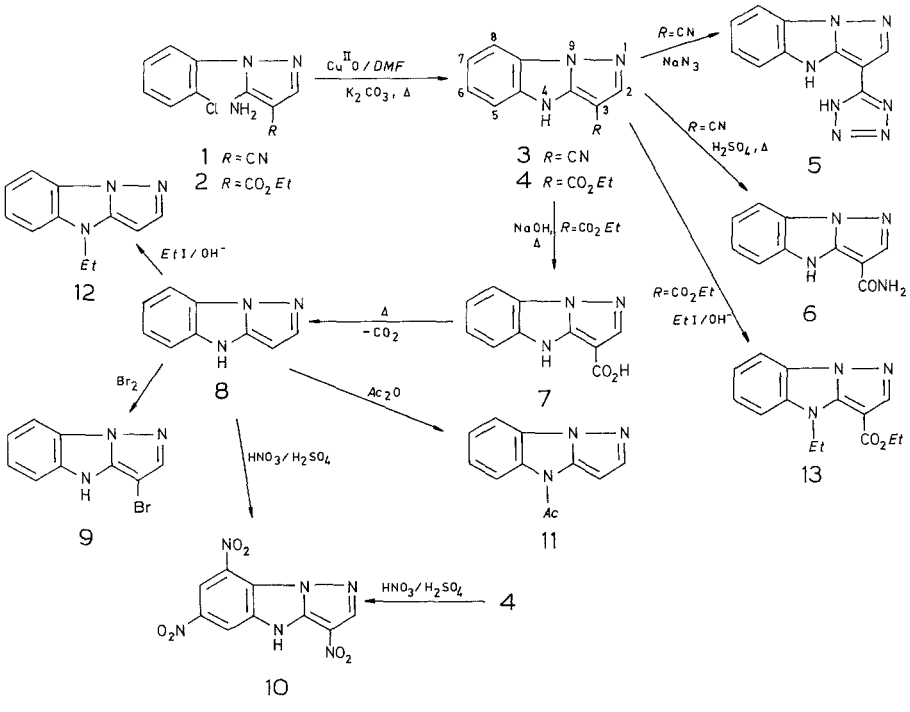

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Table 1. *Data for 4H-pyrazolo[1,5—a]benzimidazoles*

Compd. No.	yield (%)	m.p.° (from)	Molecular formula[a]	IR (cm^{-1})	PMR δ/ppm (*J* in Hz) (solvent)
3	15	281-282 (*Me*OH)	$C_{10}H_6N_4$	3250, 3210 (br. NH); 2230 (C≡N)	3.00-4.50 (NH and H_2O); 7.00-7.50 (3H, m, H-5, H-6 and H-7); 7.78 (1H, m, H-8); 8.08 (1H, s, H-2). (*DMSO-d*$_6$).
4	42	171-172 (*DMF*-H_2O)	$C_{12}H_{11}N_3O_2$	3240, 3200 (br. NH); 1670 (C=O)	1.40 (3H, t, $J = 6.75$, CH_3); 4.38 (2H, q, $J = 6.75$, CH_2); 6.99-7.49 (3H, m, H-5, H-6 and H-7); 7.84 (1H, m, H-8); 8.12 (1H, s, H-2); 10.04 (1H, br. NH). ($CDCl_3$).
5	38	278-280 (*Me*OH)	$C_{10}H_7N_7$	3500-2500 (br. NH)	4.00-6.00 (br. NH and H_2O); 7.00-7.70 (3H, m, H-5, H-6 and H-7); 7.82 (1H, m, H-8); 8.20 (1H, s, H-2). (*DMSO-d*$_6$).
6	18	299 (dec) (*Me*OH-H_2O)	$C_{10}H_8N_4O$	2800-3400 (br. NH, NH_2); 1665 (C=O)	6.70-7.50 (5H, H-5, H-6, H-7 and NH_2); 7.65 (1H, m, H-8); 8.12 (1H, s, H-2); 12.06 (1H, br. NH). (*DMSO-d*$_6$).
7	74	210-212 (*Me*OH-H_2O)	$C_{10}H_7N_3O_2$	3300-2500 (br. NH and CO_2H); 1680, 1650-1630 (br. C=O)	2.79-4.19 (br. CO_2H and H_2O); 6.99-7.59 (3H, m, H-5, H-6 and H-7); 7.77 (1H, m, H-8); 7.97 (1H, s, H-2); 12.29 (1H, br, NH). (*DMSO-d*$_6$).
8	90	220 [b]	$C_9H_7N_3$	3240-2500 (br. NH)	5.72 (1H, d, H-3, $J = 2.25$); 6.90-7.50 (3H, m, H-5, H-6 and H-7); 7.55-7.80 (1H, m, H-8); 7.62 (1H, d, $J = 2.25$, H-2); 11.30 (1H, br. NH). (*DMSO-d*$_6$).

9	80	214-215 (dec) (*Me*OH)	$C_9H_6BrN_3$	3300-2500 (br. NH)	6.99-7.69 (3H, m, H-5, H-6 and H-7); 7.71-7.89 (1H, m, H-8); 7.81 (1H, s, H-2); 11.99 (1H, br. NH). (*DMSO-d*$_6$).
10	27	296-297 [b]	$C_9H_4N_6O_6$	3380-2940 (br. NH); 1540 and 1350 (NO_2)	8.40 (1H, s, H-2); 8.68 (1H, d, $J = 2.50$, H-6); 8.93 (1H, d, $J = 2.50$, H-8). (*HMPA*).
11	69	141.5-142.5 (pet. ether)	$C_{11}H_9N_3O$	1720, 1690 (C=O)	2.47 (3H, s, CH_3); 5.92 (1H, d, $J = 2.25$, H-3); 6.97-7.47 (2H, m, H-6 and H-7); 7.67 (1H, d, $J = 2.25$, H-3); 7.77 (1H, m, H-8); 8.30 (1H, m, H-5). ($CDCl_3$).
12	16	[c]	$C_{17}H_{14}N_6O_7$	—	1.21 (3H, t, $J = 7.50$, CH_3); 3.83 (2H, q, $J = 7.50$, —CH_2); 5.53 (1H, d, $J = 2.25$, H-3); 6.71-7.26 (3H, m, H-5, H-6 and H-7); 7.61 (1H, d, $J = 2.25$, H-2); 7.51-7.81 (1H, m, H-8). ($CDCl_3$).
13	39	66.5-67.5 (*DMSO*-H_2O)	$C_{14}H_{15}N_3O_2$	1680 (C=O)	1.32 (3H, t, $J = 7.50$, N—CH_2—CH_3); 1.38 (3H, t, $J = 6.75$, O—CH_2—CH_3); 4.26 (2H, q, $J = 7.50$, N—CH_2—CH_3); 4.62 (2H, q, $J = 6.75$, O—CH_2—CH_3); 7.00-7.40 (3H, m, H-5, H-6 and H-7); 7.60-7.90 (1H, m, H-8); 8.04 (1H, s, H-2). ($CDCl_3$).

[a] Elemental analyses are in full agreement with the calculated values.
[b] Purified by sublimation.
[c] Characterized as its picrate.

Experimental

The proton magnetic resonance spectra (PMR) were obtained on a Hitachi Perkin-Elmer model R-20 B spectrometer operating at 60 MHz (*TMS* as internal standard). The infrared (IR) absorption spectra were taken by the Perkin-Elmer model 727 spectrophotometer. The solid samples were measured in potassium bromide disks while the liquid samples were run as thin films. Melting points (mp) were determined with a Fisher-Johns apparatus and are uncorrected. Elemental analyses were determined on a Perkin-Elmer model 240.

Various 4*H*-pyrazolo[1,5—*a*]benzimidazoles, obtained during this work, and their spectral characteristics are presented in Table 1.

4H-Pyrazolo[1,5—a]benzimidazole-3-carbonitrile (**3**)

A stirred mixture of 10 g of **1**, 6.4 g of anhydrous potassium carbonate, 0.18 g of copper(II) oxide in 50 ml of *N*,*N*-dimethylformamide was heated under reflux for 26 h. The solvent was removed *in vacuo* and the residue diluted with water and extracted with chloroform. The residue obtained on evaporation of chloroform was chromatographed on neutral alumina. On elution with dichloromethane **3** was obtained which was further purified by crystallization.

Ethyl 4H-pyrazolo[1,5—a]benzimidazole-3-carboxylate (**4**)

A mixture of 15 g of **2**, 7.8 g of anhydrous potassium carbonate, 0.27 g of copper(II) oxide in 45 ml of *N*,*N*-dimethylformamide was heated under reflux for 74 h, the solvent removed and the residue diluted with water and filtered. The filtrate was left overnight to form a precipitate which was filtered and crystallized to give **4**.

3-(Tetrazol-5'-yl)-4H-pyrazolo[1,5—a]benzimidazole (**5**)

The method of *Finnegan, Henry* and *Lofquist*[16] was used for the preparation of **5**. A mixture of 0.36 g of **3**, 0.14 g of sodium azide and 0.12 g of ammonium chloride in 10 ml of *N*,*N*-dimethylformamide was heated under reflux for 20 h (anhydrous conditions). The reaction mixture after cooling was filtered and the filtrate poured over crushed ice. The precipitate formed was filtered off and crystallized to give 0.17 g of **5**.

4H-Pyrazolo[1,5—a]benzimidazole-3-carboxamide (**6**)

A mixture of 0.2 g of **3** in 6 ml of sulfuric acid was heated at 40–50° for 4 h added to ice water and the precipitate filtered, washed with water and sodium carbonate solution to give 0.04 g of **6** which was purified by crystallization.

4H-Pyrazolo[1,5—a]benzimidazole-3-carboxylic acid (**7**)

The ester (**4**) was hydrolyzed by 10% sodium hydroxide solution. From 2.5 g of **4**, there was obtained 1.6 g of **7**.

4H-Pyrazolo[1,5—a]benzimidazole (**8**)

The acid (**7**) (1.12 g) was decarboxylated by heating at 180–190° (oil bath) in a sublimator under reduced pressure (2–5 mm Hg) and 1.12 g of **8** was collected from the cold finger.

3-Bromo-4H-pyrazolo[1,5—a]benzimidazole (**9**)

Bromine (0.17 ml) was added dropwise to a solution of 0.47 g of **8** in 5 ml of acetic acid at 50-60°. The reaction mixture was stirred for further 20 min and then poured over crushed ice. The precipitate was filtered, washed with water and crystallized to give 0.57 g of **9**.

3,6,8-Trinitro-4H-pyrazolo[1,5—a]benzimidazole (**10**)

A mixture of 5 ml of nitric acid and 5 ml of sulfuric acid was added to a solution of 0.5 g of **8** in 5 ml of sulfuric acid and the mixture heated at 60-65° for 1 h. The reaction mixture was poured over crushed ice and the precipitate filtered and washed with water. The resulting 0.24 g of the trinitro product (**10**) was purified by sublimation at 190-200°/3-5 mm Hg.

4-Acetyl-4H-pyrazolo[1,5—a]benzimidazole (**11**)

A mixture of 0.15 g of **8** and 4 ml of acetic anhydride was stirred at room temperature for 1 h and then poured over crushed ice. The precipitate was filtered off and crystallized from light petroleum to give 0.13 g of **11**.

4-Ethyl-4H-pyrazolo[1,5—a]benzimidazole (**12**)

To 5 ml of dry dimethylsulfoxide 0.61 g of pulverized potassium hydroxide was added followed by 0.38 g of **8**. The mixture was then stirred for 1 h at room temperature when 0.38 g of ethyl iodide was added and the agitation carried on for further 45 min; at the end of this period the reaction mixture was diluted with water and extracted with ether. The oily residue obtained on evaporating the solvent was chromatographed on silica gel (dichloromethane as eluent) to afford 0.07 g of **12** as a liquid which was characterized as its picrate, m.p. 206-208° (dec.) (*Et*OH).

Ethyl 4-ethyl-4H-pyrazolo[1,5—a]benzimidazole-3-carboxylate (**13**)

Under the conditions employed for the alkylation of **8** above, from 0.23 g of **4** there was obtained 0.1 g of **13**.

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