The Reactivity of 2,3-Diaminopyridine toward Alkyl Chloroformates and Dicarbonates

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The reaction of 2,3-diaminopyridine (DAP) with alkyl chloroformates and dialkyl dicarbonates is affected by the nature of the acylating agent and the acylation conditions. Mono and dicarbamates of DAP were obtained using chloroformates, while the formation of alkoxycarbonyl derivatives of imidazo[4,5-*b*]pyridin-2-one was observed when the reaction with dicarbonates was performed at room temperature in THF-pyridine. Our procedure for the synthesis of imidazopyridin-2-ones represents an improvement over the previous methods which require rather severe conditions. The revised structure for a monoacetyl derivative of the above bicyclic system is also reported.

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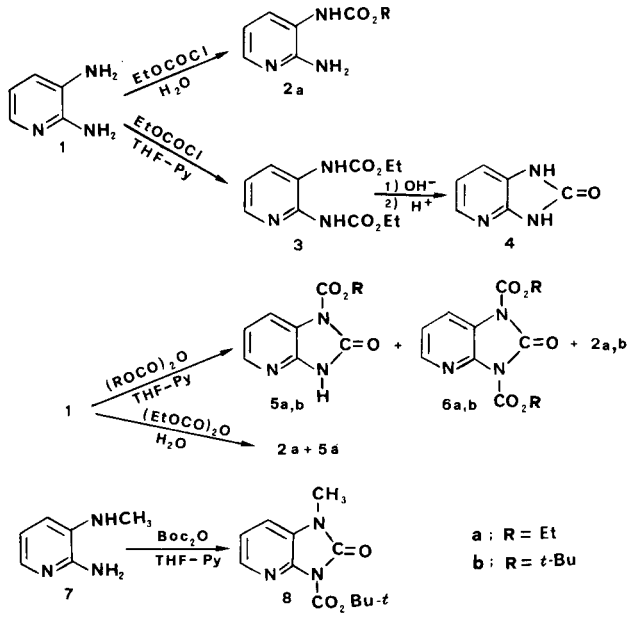
Several new imidazo[4,5-*b*]pyridin-2-one derivatives were recently found to possess pharmacological activities: cardiotonic [1a], hypotensive and antiarrhythmic [1b], antiulcer and antisecretory [1c]. Methods of synthesis for these compounds have been reported. The treatment of *N*-substituted-2,3-diaminopyridines with diethyl dicarbonate at high temperature is a practicable route to this condensed bicyclic system [2]. The intermediate formation of an urethane derivative was postulated by Yutilov [2] on the basis of the analogous behaviour of 2-amino-3-(ethoxycarbonylamino)pyridine (**2a**) under similar conditions [3]. Cyclization to imidazo[4,5-*b*]pyridin-2-ones was also performed by refluxing the intermediate ethyl carbamates in an ethanolic solution of sodium ethoxide [1c].

Because the conditions of synthesis from the literature are rather severe, we sought a milder method for the preparation of the imidazopyridin-2-ones. Therefore the reaction of 2,3-diaminopyridine (**1**) (DAP) with alkyl chloroformates and dialkyl dicarbonates in protic and aprotic media was investigated.

Treatment of DAP with ethyl chloroformate in water in an ice bath afforded the monocarbamate **2a** (57%) as the only discernible acylation product. The preparation of the above derivative by the older method [3] is more laborious. Our result is similar to that arising from the reaction of DAP with phenyl chloroformate in dioxane at 80° [4], and agrees with the reactivity of **1** and related polyamines toward aromatic aldehydes [5] and α-dicarbonyl compounds [6]. When the above condensations are performed under neutral or mild acidic conditions the 3-amino group is preferentially attached.

The dicarbamate **3** was the predominant product when the acylation with ethyl chloroformate was performed in tetrahydrofuran (THF)-pyridine (Py). In this case both the amino groups of DAP were acylated by the chloroformate which in THF-Py is more reactive than in water. On the other hand we have recently described [7] the applications

Scheme 1



of 2-amino-3-(benzyloxycarbonylamino)pyridine, the main product isolated from the reaction of DAP with benzyl chloroformate in the above aprotic conditions. Alkaline hydrolysis of **3** as described for the corresponding dicarbamate of *o*-phenylendiamine [8] afforded 1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (**4**).

Interestingly with diethyl or di-*t*-butyl dicarbonates as acylating agents in THF-Py, a quite different reaction was observed. In fact alkoxycarbonyl-1,3-dihydro-2*H*-imidazo-[4,5-*b*]pyridin-2-ones **5a,b** and **6a,b** were isolated as the main products. Small amounts of 2-amino-3-(alkoxycarbonylamino)pyridines were also obtained.

As expected an analogous treatment of 2-amino-3-(methylamino)pyridine (**7**) with di-*t*-butyl dicarbonate(Boc_2O) gave 1-methyl-3-*t*-butoxycarbonyl-1,3-dihydro-2*H*-imidazo-[4,5-*b*]pyridin-2-one (**8**) (84%). It is noteworthy that at-

tempts to cyclize the probable intermediate **2a** in THF-Py, in the absence of diethyl dicarbonate, failed. The role of dialkyl dicarbonates in the formation of imidazopyridin-2-ones was not further clarified.

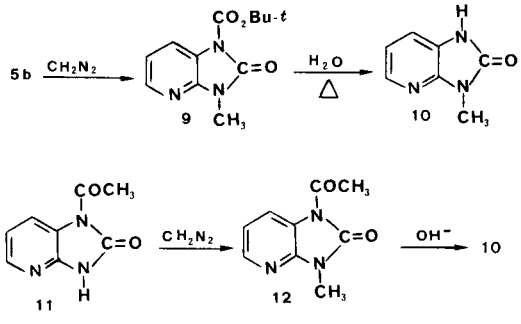
Finally acylation of **1** with diethyl dicarbonate in water in an ice bath afforded a mixture of **2a** (29%) and **5a** (10%).

The structure of the bicyclic derivatives **5**, **6** and **8** was inferred from analytical and spectroscopic data. The 1-position of the alkoxycarbonyl group in **5a,b** was suggested by the downfield resonance of C-7 proton (C-4 of pyridine) and then confirmed by the following chemical transformation. Methylation of **5b** with diazomethane afforded 1-*t*-butoxycarbonyl-3-methyl-1,3-dihydro-2*H*-imidazo [4,5-*b*]pyridin-2-one (**9**), which was then hydrolyzed to the methyl derivative **10** by boiling water. Compound **10** was identified by comparison of melting point, ir and nmr spectra to those of an authentic sample [2].

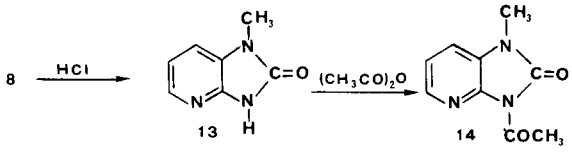
The diacyl derivative **6b** can be easily converted into **5b** by stirring in a THF solution containing 2*N* hydrochloric acid, while complete hydrolysis to **4** can be performed in hot water. In the light of these data on the different stability of the two *N*-COOR bonds under hydrolytic conditions, the previous assignment (3-acetyl) for some imidazo[4,5-*b*]-pyridin-2-ones of biological interest [1b] seemed incorrect to us. In fact ^{1}H nmr spectrum of the monoacetyl derivative **11** prepared by the method of Harrison and Smith [9] exhibited the characteristic lowfield resonance of 7-H showed by **5a** and **5b**. Our hypothesis was then confirmed by a chemical correlation analogous to that for **5b**.

Furthermore, acetylation of 1-methyl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (**13**) obtained by acidic hydrolysis of **8** afforded the acetyl derivative **14**, which showed a nmr spectrum different from that of isomer **12**.

Scheme 2



Scheme 3



1-Alkyl-3-acyl- and 1-acyl-3-alkyl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-ones are not always reliably distinguished on the basis of the resonance position of C-7 proton. In fact the presence of an acyl group at *N*-1 causes a downfield shift of 7-H signal, while an opposite effect is showed by an alkyl group. Similar shifts on the above signal have not been observed after the introduction of an acyl or an alkyl group at the *N*-3 position.

In conclusion an overall analysis of our results indicates that the nature of the acylating agent rather than the reaction conditions strongly influenced the DAP acylation out-

Table

^{1}H-NMR Data (δ) for Imidazo[4,5-*b*]pyridin-2-one Derivatives [a]

Compound	Pyridine Protons [b]			Other Signals
	α-H	β-H	γ-H	
4	7.97	7.04	7.37	
5a	8.13	7.13	7.94	1.38 (3H, t, J = 7 Hz, CH_2CH_3), 4.44 (2H, q, J = 7 Hz, CH_2-CH_3)
5b	8.20	7.08	8.04	1.65 (9H, s, $C(CH_3)_3$)
6a	8.32	7.19	8.16	1.45 (6H, t, J = 7 Hz, two CH_2-CH_3), 4.52 and 4.54 (4H, two q, J = 7 Hz, two CH_2-CH_3)
6b	8.34	7.20	8.13	1.65 (18H, s, two $C(CH_3)_3$)
8	8.24	7.19		1.66 (9H, s, $C(CH_3)_3$), 3.38 (3H, s, N-CH_3)
9	8.16	7.04	8.00	1.66 (9H, s, $C(CH_3)_3$), 3.45 (3H, s, N-CH_3)
10	8.04	7.06	7.39	3.43 (3H, s, N-CH_3)
11	8.14	7.11	8.37	2.71 (3H, s, CO-CH_3)
12	8.20	7.08	8.35	2.72 (3H, s, CO-CH_3), 3.46 (3H, s, N-CH_3)
13	8.14	7.04	7.19	3.42 (3H, s, N-CH_3)
14	8.29	7.20		2.77 (3H, s, CO-CH_3), 3.39 (3H, s, N-CH_3)

[a] Methanol-d_4 solutions for **4** and **10**; DMSO-d_6 solution for **5a**; deuteriochloroform-methanol-d_4 solution (1:1) for **11**. [b] *Ortho* (α-H), *meta* (β-H) and *para* (γ-H) protons occur as double doublets ($J_{\alpha,\beta}$ = 5 Hz, $J_{\beta,\gamma}$ = 8.5 Hz, $J_{\alpha,\gamma}$ = 1.5 Hz); the chemical shifts of β- and γ-H are in compounds **8** and **14** very similar and the mid point of the resulting multiplet is given.

comes. The main interest of this investigation lies, in our opinion, in the synthesis of imidazo[4,5-*b*]pyridin-2-one derivatives under mild conditions. Furthermore the facile cleavage of 3-Boc group permits the selective introduction of an acyl or alkyl group at the *N*-3 atom of **4**.

EXPERIMENTAL

Melting points were determined with a Büchi oil bath apparatus and are uncorrected. Infrared spectra (potassium bromide) were recorded with Perkin-Elmer 521 and 983 spectrophotometers. The ^{1}H nmr spectra were measured with a Varian EM-390 spectrometer using, unless otherwise specified, deuteriochloroform as the solvent (TMS as the internal standard). The coupling constants of resolved pyridine signals for all described compounds are those reported at footnote of table. Merck silica gel 60 (230-400 mesh) and Woelm basic alumina (Brockmann IV) were used for column chromatography. Preparative layer chromatography (plc) was carried out with Merck F_{254} silica gel in dichloromethane-methanol (95:5), unless otherwise specified. Light petroleum refers to the 40-60° bp fraction. The drying agent used was sodium sulfate. Dry pyridine (Py) and tetrahydrofuran (THF) were used.

Reaction of DAP with Ethyl Chloroformate in Water.

To a stirred solution of DAP (0.655 g, 6 mmoles) in water (14 ml), cooled in an ice bath, ethyl chloroformate (1.15 ml, 12 mmoles) was added. Cooling and stirring were continued for 5 hours, and then the reaction mixture was evaporated under *vacuum* without heating. The residue was chromatographed on a silica column (1:40); elution with dichloromethane-methanol (95:5) afforded 2-amino-3-(ethoxycarbonylamino)pyridine (**2a**) (0.616 g, 57%), mp 94-95° (ether), lit 97.5° (benzene) [3]; ir: 3420, 1705, 1685, 1460 cm^{-1}; nmr: δ 1.27 (3H, t, J = 7 Hz, CH_2-CH_3), 4.23 (2H, d, J = 7 Hz, CH_2CH$_3$), 6.70 (1H, dd, 5-H), 7.60 (1H, dd, 4-H), 7.96 (1H, dd, 6-H). The ir and nmr spectra of **2a** were identical to those of a sample prepared by the method of Clark-Lewis and Thompson [3].

Reaction of DAP with Diethyl Dicarbonate in Water.

To a stirred solution of DAP (0.655 g, 6 mmoles) in water (14 ml), cooled in an ice bath, diethyl dicarbonate (1.7 ml, 12 mmoles) was added. After cooling and stirring for 5 hours, the reaction mixture was evaporated under *vacuum* without heating. The residue was chromatographed on a silica column (1:40); elution with dichloromethane-methanol (95:5) afforded 1-ethoxycarbonyl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (**5a**) (0.129 g, 10%). Further elution gave **2a** (0.32 g, 29%) [10].

Compound **5a** had mp 201-201.5° (ethyl acetate); ir: 1770, 1725, 1335 cm^{-1}.

Anal. Calcd. for $C_9H_9N_3O_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.12; H, 4.41; N, 20.24.

Reaction of DAP with Ethyl Chloroformate in THF-Py.

To a stirred suspension of **1** (2 mmoles) in THF (4 ml) and Py (0.65 ml), cooled at 0°, ethyl chloroformate (4 mmoles) was added dropwise. After stirring at 0° for 15 minutes and at room temperature for 3 hours, ethyl acetate was added in excess. The organic phase was washed with water, dried and evaporated under *vacuum*. The residue was chromatographed on a column of alumina (1:30). Elution with dichloromethane-ethyl acetate (9:1) gave 0.41 g (81%) of 2,3-bis(ethoxycarbonylamino)pyridine (**3**) and 0.015 g (4.1%) of **2a** [10].

Compound **3** had mp 92-92.5° (ether); ir: 3193, 1727, 1604 cm^{-1}; nmr: δ 1.27 and 1.30 (6H, two t, two CH_2-CH_3), 4.21 and 4.28 (4H, two q, two CH_2-CH$_3$), 7.19 (1H, dd, 5-H), 8.20 (1H, br d, 6-H), 8.26 (1H, dd, 4-H), 8.57 and 9.78 (2H, two s, two NH).

Anal. Calcd. for $C_{11}H_{15}N_3O_4$: C, 52.17; H, 5.97; N, 16.59. Found: C, 52.20; H, 6.06; N, 16.48.

Reaction of DAP with Diethyl Dicarbonate in THF-Py. Experiment A.

To a stirred suspension of DAP (2 mmoles) in THF (4 ml) and Py (0.32 ml), cooled at 0°, diethyl dicarbonate (4 mmoles) was added. After stirring at 0° for 15 minutes and at room temperature for 3 hours, ethyl acetate was added in excess. The organic layers were washed with water, dried and evaporated under *vacuum*. The residue was chromatographed on plc to afford 1,3-diethoxycarbonyl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (**6a**) (0.09 g, 16%), **5a** (0.11 g, 27%) [10] and **2a** (0.02 g, 5.5%) [10].

Compound **6a** had mp 130-131° (dichloromethane-ether); ir: 1780, 1752, 1430 cm^{-1}.

Anal. Calcd. for $C_{12}H_{13}N_3O_5$: C, 51.61; H, 4.69; N, 15.05. Found: C, 51.45; H, 4.79; N, 14.98.

Experiment B.

In another attempt, carried out in the above conditions, 6 mmoles of dicarbonate and 2 mmoles of DAP were employed. Usual work up gave a residue which was chromatographed on plc to give **6a** (0.19 g, 34%) [10], **5a** (0.067 g, 16%) [10] and **2a** (0.025 g, 6.9%) [10].

Reaction of DAP with Boc_2O in THF-Py.

Treatment of 2 mmoles of DAP with Boc_2O (4 mmoles) as described in experiment A afforded, after usual work up and plc, 1,3-di-*t*-butoxycarbonyl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (**6b**) (0.237 g, 35%), 1-*t*-butoxycarbonyl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (**5b**) (0.082 g, 17%) and 2-amino-3-(*t*-butoxycarbonylamino)pyridine (**2b**) (0.085 g, 20%).

Compound **6b** had mp 95° (ether-light petroleum); ir: 1805, 1740, 1428 cm^{-1}.

Anal. Calcd. for $C_{16}H_{21}N_3O_5$: C, 57.30; H, 6.31; N, 12.53. Found: C, 57.26; H, 6.28; N, 12.43.

Compound **5b** had mp 156-157° (ether); ir: 1755, 1723, 1448 cm^{-1}.

Anal. Calcd. for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.86. Found: C, 56.23; H, 5.55; N, 17.79.

Compound **2b** had mp 142-143° (ether-light petroleum); ir: 3135, 1673, 1455 cm^{-1}; nmr: δ 1.47 (9H, s, C(CH_3)$_3$), 6.66 (1H, dd, 5-H), 7.62 (1H, dd, 4-H), 7.95 (1H, dd, 6-H).

Anal. Calcd. for $C_{10}H_{15}N_3O_2$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.50; H, 7.21; N, 20.11.

The following product distribution was observed when the reaction was performed with 2 mmoles of DAP and 6 mmoles of Boc_2O as in experiment B: **6b** (0.448 g, 67%) [10], **5b** (0.02 g, 4.2%) [10], and **2b** (0.057 g, 14%) [10].

1-Methyl-3-*t*-butoxycarbonyl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (**8**).

To a stirred solution of **7** [7] (1 mmole) in THF (2 ml) and Py (0.16 ml), cooled at 0°, Boc_2O (3 mmoles) was added. After stirring at 0° for 15 minutes and at room temperature for 3 hours, the mixture was partitioned between ethyl acetate and water. Evaporation of the organic phase gave a residue which was chromatographed on a column of silica (12 g). Elution was performed with dichloromethane and then dichloromethane-ether (9:1) to give the title compound **8** (0.208 g, 84%), mp 55-56° (ether); ir: 1785, 1750, 1369 cm^{-1}.

Anal. Calcd. for $C_{12}H_{15}N_3O_3$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.68; H, 6.00; N, 16.86.

Conversion of the Dicarbamate **3** to **4**.

Following the procedure of Darapsky and Gaudian [8], 0.09 g of **3** were dissolved in 2*N* sodium hydroxide (3 ml) by warming at 50°. The solution was cooled at room temperature and acidified with 6*N* hydrochloric acid. After neutralization with saturated aqueous sodium bicarbonate, ethyl acetate was added. The organic layers were washed with water, dried and evaporated to give pure **4** (0.044 g, 92%); ir: 3462, 1692, 1434 cm^{-1} [11].

Formation of 3-Methyl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (**10**) from **5b**.

A solution of **5b** (0.08 g) in ethyl acetate (5 ml)-methanol (0.5 ml), cooled in an ice bath, was treated with ethereal diazomethane and stirred for 45 minutes. Evaporation under reduced pressure gave a residue which

was purified by tlc [dichloromethane-ether (8:2) as eluant] to afford 0.064 g of **9**, mp 99.5-100° (ether); ir: 1797, 1752, 1373 cm^{-1}.

Anal. Calcd. for $C_{12}H_{15}N_3O_3$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.80; H, 6.17; N, 16.76.

Derivative **9** (0.062 g) was refluxed in water (2 ml) for 30 minutes. Extraction with ethyl acetate and evaporation of the organic layer afforded pure **10** in quantitative yield, mp 236-239° (ethanol) (with a Kofler hot-stage apparatus), lit 235-236° [2]; ir: 3016, 1719, 1380 cm^{-1} [11].

Formation of **10** from 1-Acetyl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (**11**).

Compound **11** [9] (0.048 g) in ethyl acetate (5 ml)-methanol (0.5 ml), cooled in an ice bath, was stirred with ethereal diazomethane for 15 minutes. After evaporation, the residue was purified on plc to give 1-acetyl-3-methyl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (**12**) (0.044 g), mp 119-120° (ether); ir: 1760, 1747, 1483, 1370 cm^{-1}.

Anal. Calcd. for $C_9H_9N_3O_2$: C, 56.54; H, 4.75; N, 21.98. Found: C, 56.70; H, 4.80; N, 21.81.

Compound **12** (0.044 g) was heated in 0.5*N* sodium hydroxide (4 ml) at 70° for 20 minutes and then cooled at room temperature. After neutralization with 2*N* hydrochloric acid and solid sodium bicarbonate, usual extraction with ethyl acetate and plc purification of the resulting residue gave **10** (0.032 g, 93%) [11].

Hydrolysis of **6b** to **5b**.

A solution of **6b** (0.1 g) in THF (5 ml) containing 2*N* hydrochloric acid (5 ml) was stirred at room temperature for 4 hours. Solid sodium carbonate and ethyl acetate were added, the organic phase was washed with water, dried and evaporated to give pure **5b** (0.051 g, 73%) [10].

Complete hydrolysis of **6b** to **4** [11] was performed in boiling water as described for the conversion of **9** to **10**.

Synthesis of 1-Methyl-3-acetyl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (**14**).

Acidic hydrolysis of **8**, performed as in the case of **6b**, afforded **13** in 84% yield, mp 201-202° (methanol), lit 200-201° (benzene) [2]; ir: 3034, 1715, 1392 cm^{-1}.

Compound **13** (1 mmole) was then refluxed in acetic anhydride (1 ml) for 30 minutes. The mixture was evaporated under *vacuum* to give pure **14** in quantitative yield, mp 118.5-119.5° (THF-dry ether); ir: 1729, 1458, 1375 cm^{-1}.

Anal. Calcd. for $C_9H_9N_3O_2$: C, 56.54; H, 4.75; N, 21.98. Found: C, 56.39; H, 4.80; N, 21.90.

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[10] The ir and nmr spectra were identical to those of the earlier characterized sample.

[11] The ir and nmr spectra of **4** and **10** were identical to those of samples prepared by the methods of Yutilov and Svertilova [2].