COMPARED REACTIVITY OF 3-, 5-, 6-, AND 8-AMINOIMIDAZO[1,2-*a*]PYRIDINES IN COMBES REACTION: ACCESS TO IMIDAZONAPHTHYRIDINES AND DIPYRIDO[1,2-*a*:3',2'-*d*]IMIDAZOLE

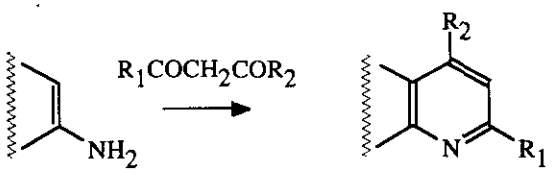
Yves Blache,[1] Alain Gueiffier*,[1] Olivier Chavignon,[2] Henry Viols,[1] Jean Claude Teulade,[2] and Jean Pierre Chapat[1]

Laboratoire de Chimie Organique Pharmaceutique, URA-CNRS 1111, 15 Avenue Charles Flahault, Faculté de Pharmacie, 34000 Montpellier, France,[1] Laboratoire de Chimie Organique Pharmaceutique, Groupe de Recherche en Pharmacochimie, UFR de Pharmacie, 28 Place H. Dunant, B.P. 38, 63001 Clermont-Ferrand, France[2]

Abstract- The synthesis of imidazo[1,2-*a*][1,8]naphthyridines and dipyrido[1,2-a:3',2'-*d*]imidazole by treatment of aminoimidazo[1,2-*a*]pyridines following the Combes procedure is described.

The Combes procedure is a usefull synthetic method for the construction of heterocyclic compounds, particullary used for the preparation of 1,8-naphthyridines from 2-aminopyridines.[1] Extension of this procedure to varied amino-heterocycles is of an interest for facile construction of polycondensed heterocyclic systems (Scheme 1).

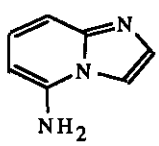
Scheme 1



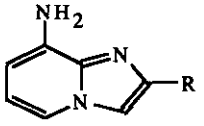
In continuation of our studies on the reactivity of the imidazo[1,2-*a*]pyridine ring system, we investigated a new approach, based on the Combes procedure, for the synthesis of imidazonaphthyridines and dipyridoimidazoles. Synthesis of starting materials (**1-5**) was achieved according to the published methods for compound (**1**),[2] (**2a**),[3] (**2b**),[4] (**3**),[5] (**4a**),[6] (**4c, 5c**).[7] Ethyl 5-methyl-6-nitroimidazo[1,2-*a*]pyridine-2-carboxylate (**4b**) was obtained by treatment of 6-amino-3-nitro-2-picoline[8] with ethyl bromopyruvate in

refluxing ethanol. Tin/hydrobromic acid mediated reduction of **4a** and **4b** gave respectively **5a** and **5b** (Scheme 2).

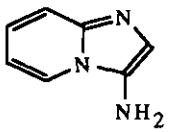
Scheme 2



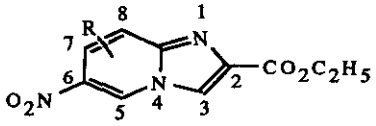
(1)



(2a) R = H
(2b) R = $CO_2C_2H_5$

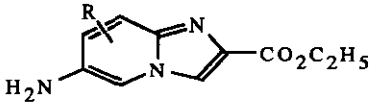


(3)



(4a) R = H
(4b) R = 5-CH_3
(4c) R = 7-CH_3

Sn / HBr / -5 °C

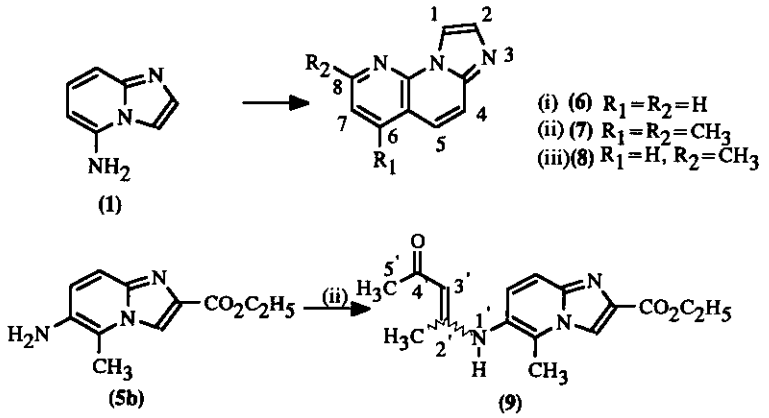


(5a) R = H
(5b) R = 5-CH_3
(5c) R = 7-CH_3

We have first investigated the reactivity of the pyridine ring of **1**: Treatment of 5-aminoimidazo[1,2-*a*]-pyridine (**1**) with 1,1,3,3-tetramethoxypropane in refluxed phosphoric acid led to imidazo[1,2-*a*]-[1,8]naphthyridine (**6**) in an 11% yield. Comparatively 6,8-dimethyl derivative (**7**) and 8-methyl derivative (**8**) were obtained in 64% and 32% yields respectively (Scheme 3). ^{1}H-Nmr spectrum of **6-7** were in accord with those previously described.[9] ^{1}H-Nmr spectra of **8** at 100 MHz showed an AB system at δ 7.44 (J = 6.9 Hz) corresponding to H-4 and H-5, two doublets at δ 7.26 and 7.96 (J = 8.1 Hz) for H-7 and H-6 respectively, while the signals of H-1 and H-2 appeared as two singlets (respectively δ 8.43 and 7.60). This determination was confirmed by ^{13}C-nmr with a signal at δ 24.87 for the methyl group, four quaternary carbon and six CH. From these results, 2,4-pentanedione which gives the best yield, was used for the rest of this work. When the reaction was carried out with the 8-amino derivatives (**2a-b**), no reaction took place and starting material was recovered unchanged. Using ethyl 6-aminoimidazo[1,2-*a*]pyridine-2-carboxylate (**5a**), no more cyclisation occurred. When this amino group was activated with a methyl group at the C-5 position (**5b**), the reaction led to the intermediary enaminone (**9**). ^{1}H-Nmr of **9** showed a singlet at δ 5.11 attribuable to H-3', an AB system at δ 7.15 (J = 9.6 Hz) for H-7 and H-8, a singlet at δ 8.00 for H-3 and a singlet at δ 11.94 (NH). Proof of the structure was found by ^{13}C-nmr which showed the characteristic signals of enaminone (δ 97.7 for C-3', δ 161.2 for C-2', and δ 197.1 for C-4'). Overwise, when the methyl group is

placed on the C-7 position (**5c**), no reaction occurred (Scheme 3).

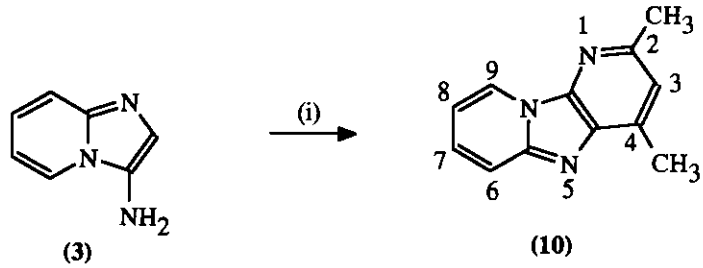
Scheme 3



(i) $(CH_3O)_2CH_2CH(OCH_3)_2$, H_3PO_4, reflux ; (ii) $CH_3COCH_2COCH_3$, H_3PO_4, reflux
(iii) $CH_3COCH_2CH(OCH_3)_2$, H_3PO_4, reflux

Finally, we investigated the reactivity of the imidazolyl moiety: treatment of the 3-amino derivative (**3**) in the described condition led to the formation of 2,4-dimethyldipyrido[1,2-*a*:3',2'-*d*]imidazole (**10**) in 59%yield (Scheme 4). Structural determination of compound (**10**) was made by ^1H and ^{13}C-nmr. ^1H-Nmr spectra showed two singlets at δ 2.70 and 2.74 for the methyl groups. The two triplets at δ 7.45 and 6.87 were respectively attributed at H-7 and H-8, and H-3 appeared as a singlet at δ 7.18. This determination is confirmed by ^{13}C-nmr and by comparison with the unsubstituted structure.[10]

Scheme 4



(i) $CH_3COCH_2COCH_3$, H_3PO_4, reflux

In conclusion, the Combes reaction is a usefull method for the preparation of imidazo[1,2-*a*]-

[1,8]naphthyridines from 5-aminoimidazo[1,2-*a*]pyridines, while the access to the imidazo[1,2-*a*]-[1,5]naphthyridine series is not permitted following this process. However, this reaction is also a usefull synthetic method for the preparation of dipyrido[1;2-*a*:3',2'-*d*]imidazole series.

EXPERIMENTAL

General. Mps were determined on a Büchi capillary melting point apparatus and are not corrected. Elemental analyses were performed by Microanalytical Center, ENSCM, Montpellier. Spectral measurements were taken using the following instruments: ^{1}H-Nmr spectra were taken on a Varian EM 360 (60 MHz) or a Brüker AC 100 (100 MHz); ^{13}C-nmr spectra were obtained at 26°C with proton noise decoupling at 25 MHz with a Brüker AC 100 instrument. Chemical shifts are expressed relative to internal tetramethylsilane in $CDCl_3$ at a concentration of *ca* 5%. Mass spectra were recorded on a LKB 2091 spectrometer at 70eV [$\theta_{(source)}$=180°C]. Analycal sample of the prepared compounds were purified by high performance liquid chromatography (hplc), Waters M 590, on a preparative alumina or silica gel column. When necessary, solvents and reagents were dried prior to use. Dichloromethane was dried over activated alumina and distilled from calcium hydride. Thin layer chromatography (tlc) were performed on 0.25 mm E. Merck precoated neutral alumina plates.

*Ethyl 5-methyl-6-nitroimidazo[1,2-a]pyridine-2-carboxylate (**4b**)*. A mixture of 6-amino-3-nitro-2-picoline (10 g, 65.3 mmol) and ethyl bromopyruvate (13 g, 66.6 mmol) was stirred in refluxed ethanol (50 ml) for 4 h. After evaporation of the solvent, the brown oil was dissolved in water, basified with powder Na_2CO_3, and extracted with dichloromethane. After dryness and evaporation of the solvent, the crude product was purified by chromatography on neutral alumina (elution with dichloromethane) to give 9 g (55%) of pure **4b** ; mp 198-200°C (CH_3CN); ^{1}H-nmr ($CDCl_3$, 100 MHz) δ: 1.44 (t, J = 7.2 Hz, CH_3), 3.03 (s, CH_3), 4.48 (q, J = 7.2 Hz, CH_2), 7.79 (AB system, J = 9.7 Hz, H-7,8), 8.35 (s, H-3); *Anal.* Calcd for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.45; N, 16.86. Found: C, 52.89; H, 4.51; N, 16.79.

*Ethyl 6-aminoimidazo[1,2-a]pyridine-2-carboxylate (**5a**)*. A mixture of 6-nitroimidazo[1,2-*a*] pyridine (2 g, 8.5 mmol), tin (2 g, 16.8 mmol) in 48% hydrobromic acid (20 ml) was stirred at -5°C for 2 h. The solution was then basified with 30% aqueous ammonia and extracted three times with dichloromethane. After evaporation of solvent, the crude amine was purified by chromatography on neutral alumina (eluted with dichloromethane) to give 1.43g of **5a** (82%); mp: 169-171°C (CH_3CN); ^{1}H-nmr ($CDCl_3$, 100 MHz) δ: 1.36 (t, J = 6.9 Hz, CH_3), 3.57 (s, NH_2), 4.38 (q, J = 6.9 Hz, CH_2), 7.16 (AB system, J = 8.3 Hz, H-

7,8), 7.53 (s, H-5), 7.94 (s, H-3). *Anal.* Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.32; H, 5.32; N, 20.51.

Ethyl 6-amino-5-methylimidazo[1,2-a]pyridine-2-carboxylate (5b). Using the general procedure given for reduction of nitro derivatives, **5b** was obtained in 89% yield; mp: 148-150°C (MeOH); ^{1}H-nmr ($CDCl_3$, 100 MHz) δ: 1.43 (t, J = 7.2 Hz, CH_3), 2.43 (s, CH_3), 3.46 (s, NH_2), 4.45 (q, J = 7.2 Hz, CH_2), 7.18 (AB system, J = 9.6 Hz, H-7,8), 8.01 (s, H-3). *Anal.* Calcd for $C_{11}H_{13}N_3O_2$: C,60.26; H, 5.98; N, 19.17. Found: C, 60.35; H, 6.12; N, 19.11.

General procedure for the Combes cyclisation; imidazo[1,2-a][1,8]naphthyridine (6). A mixture of 5-aminoimidazo[1,2-*a*]pyridine (**1**) (1 g, 7.5 mmol) and 1,1,3,3-tetramethoxypropane (1.3 g, 7.9 mmol) was refluxed at 158°C in phosphoric acid (4 ml) for 2 h. After being cooled, the solution was poured on ice, neutralised with powder sodium carbonate, and extracted three times with dichloromethane. Organic layers were dried over sodium sulfate and concentrated. The resulting brown oil was chromatographed on neutral alumina (elution with dichloromethane) to give **6** (0.14 g, 11%); mp: 89-91°C [lit.,[9] 91-93°C].

6,8-Dimethylimidazo[1,2-a][1,8]naphthyridine (7). Compound (**7**) was obtained from **1** and 2,4-pentanedione following the precited procedure in a 64% yield; mp: 170-172°C [Lit.,[9] 169-171°C].

8-Methylimidazo[1,2-a][1,8]naphthyridine (8). This compound was obtained from **1** and acetyl acetaldehydedimethylacetal in a 32% yield; mp: 101-103°C (CH_3CN); ^{1}H-nmr ($CDCl_3$, 100 MHz) δ: 2.71 (s, CH_3), 7.26 (d, J = 8.1 Hz, H-7), 7.44 (AB system, J = 6.9 Hz, H-4 and H-5), 7.60 (s, H-2), 7.96 (d, J = 8.1 Hz, H-6), 8.43 (s, H-1); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ: 24.87 (CH_3), 111.74 (C-1), 115.44 (C-5a), 117.35 (C-4), 120.92 (C-5), 124.11 (C-7), 132.34 (C-2), 136.97 (C-6), 143.16 (C-9a), 144.92 (C-3a), 158.58 (C-8); *Anal.* Calcd for $C_{11}H_9N_3$: C, 72.11; H, 4.95; N, 22.94. Found: C, 71.98; H, 4.99; N, 23.03.

Ethyl 6-[4-(pent-3-ene-2-one)-yl]amino-5-methylimidazo[1,2-a]pyridine-2-carboxylate (9). Compound (**9**) was obtained from **5b** following the precited procedure in 68% yield; mp: 129-131°C (CH_3CN); ^{1}H-nmr ($CDCl_3$, 100 MHz) δ: 1.23 (t, J =7.8 Hz, CH_3), 1.61 (s, CH_3), 1.94 (s, CH_3), 4.25 (q, J =7.8 Hz, CH_2), 5.11 (s, H-3'), 7.15 (AB system, J = 9.6 Hz, H-7 and H-8), 8.00 (s, H-3), 11.94 (s, NH); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ : 13.9 (CH_3), 14.1 (CH_3), 29.1 (CH_3), 61.1 (CH_2), 97.7 (C-3'), 115.73 (C-3*), 116.2 (C-8*),

124.1 (C-5), 127.5 (C-7), 132.1 (C-2), 137.6 (C-6), 144.1 (C-8a), 161.2 (C-2'), 163.0 (CO), 197.1 (C-4'); *Anal.* Calcd for $C_{16}H_{19}N_3O_3$: C, 63.77; H, 6.36; N, 13.94. Found: C, 63,71; H, 6.26, N, 13.81.

2,4-Dimethyldipyrido[1,2-a:3',2'-d]imidazole (10). This derivative was obtained from **3** following the procedure precited in 59% yield; mp: 159-161°C (CH_3CN); ^{1}H-nmr ($CDCl_3$, 100 MHz) δ: 2.70 (s, CH_3), 2.74 (s, CH_3), 6.87 (t, J = 6.4 Hz, H-8) 7.18 (s, H-3), 7.45 (t, J = 6.4 Hz, H-7), 7.68 (d, J = 6.4 Hz, H-6), 8.76 (d, J = 6.4 Hz, H-9); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ: 16.7 (CH_3), 24.4 (CH_3), 110.6 (C-8), 118.1 (C-6), 122.5 (C-9), 124.6 (C-7), 130.1 (C-3), 139.2 (C-4a or C-4), 140.7 (C-4 or C-4a), 147.4 (C-5a), 151.7 (C-2 or C-10a), 153.3 (C-10a or C-2); *Anal.* Calcd for $C_{12}H_{11}N_3$: C, 73.07; H, 5.62; N, 21.30. Found: C,72.91; H, 5.57; N, 21.11.

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