Research on Heterocyclic Compounds. XLII. The Vilsmeier Reaction in the Synthesis of Imidazo[1,2-*a*]pyrimidine Derivatives

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The Vilsmeier reaction on imidazo[1,2-*a*]pyrimidine ring is reported. The 3-formyl derivative obtained is oxidized to yield the corresponding carboxylic acid.

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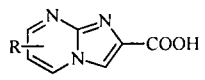
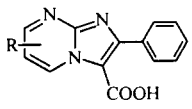
In the context of our research on the structure-*a*ctivity relationships and mode of action of bicyclic imidazo-derivatives with antiinflammatory and analgesic activity [1], we synthesized a series of imidazo[1,2-*a*]pyrimidine-2-carboxylic acids **A** (Figure 1), which showed significant antiinflammatory and analgesic action in experimental animal models, but no or negligible ulcerogenic activity on rat gastric mucosa [2].

In consideration of this interesting pharmacological profile, we have decided to synthesize a new series of analogous compounds with only one structural change, that is 2-phenylimidazo[1,2-*a*]pyrimidine-3-carboxylic acids **B** (Figure 1).



A



B

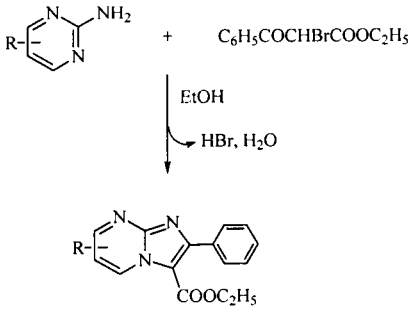
Figure 1

The insertion of a hydrophobic phenyl moiety on the imidazole ring has already displayed a favourable influence on the pharmacological activity of similar imidazo-derivatives, for example imidazo[1,2-*b*]pyridazines [3].

The synthetic method used to prepare new compounds of the type **B** is closely similar to the general procedure reported in our above mentioned papers. Such a method is based on the reaction of a heteroarylamine with an α-haloketoester: in this case, the reaction in ethanolic solution of a 2-*a*minopyrimidine with ethyl 2-benzoyl-2-bromoacetate afforded the required ethyl 2-phenylimidazo-[1,2-*a*]pyrimidine-3-carboxylates (Scheme 1), which were then converted into the corresponding carboxylic acids **B**.

The cyclocondensation reaction depicted in Scheme 1 normally gives the required products with sufficiently satisfactory yields [4]. However, only traces of the required ester were obtained when the starting amine was 2-*a*mino-4-Chloro-6-methylpyrimidine.

Scheme 1



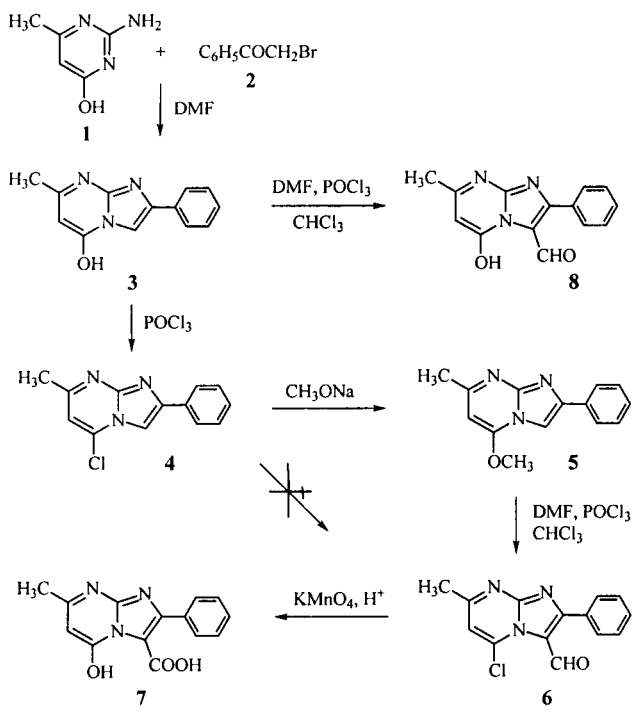
As the amount of product necessary for pharmacological tests was more, it became essential to divise a different synthetic procedure in order to obtain the required product, ethyl 5-Chloro-7-methyl-2-phenylimidazo[1,2-*a*]pyrimidine-3-carboxylate and/or the corresponding acid, with in higher yields.

This goal was reached through the synthetic route depicted in Scheme 2. The first step involved the cyclocondensation of 2-*a*mino-4-hydroxy-6-methylpyrimidine **1** with 2-bromoacetophenone **2** in refluxing dimethylformamide solution to obtain, in good yield, 5-hydroxy-7-methyl-2-phenylimidazo[1,2-*a*]pyrimidine **3**.

Compound **3** was then chlorinated with phosphorus oxychloride ($POCl_3$) to afford 5-Chloro-7-methyl-2-phenylimidazo[1,2-*a*]pyrimidine **4**. At this point, our original intention was to obtain the corresponding 3-formyl derivative **6** by means of the Vilsmeier reaction, which involved the treatment of **4** with $POCl_3$ and dimethyl formamide (DMF) in chloroform. However, the reaction did not give the product **6**. The attempt was probably unsuccessful due to the insufficient nucleophilic character of the carbon atom in position 3 because of the presence of Cl at position 5. Consequently, the Vilsmeier electrophilic reagent which was formed *in situ* during the reaction was incapable of attacking position 3.

Such explanation is supported by the studies of Pentimalli [5,6] on the reactivity of imidazo[1,2-*a*]pyrimidines bearing electron-withdrawing and electron-donating substituents on the pyrimidine ring.

Scheme 2



On these basis, we decided to replace the chlorine atom in position 5 by the electron-donating methoxyl group. The 5-methoxy derivative **5**, readily obtained by reaction of **4** with sodium methoxide in anhydrous methanol, was effectively formylated by the Vilsmeier reaction and simultaneously the methoxyl group was again substituted by chlorine, and thus obtaining the required product **6**, namely 5-Chloro-3-formyl-7-methyl-2-phenylimidazo[1,2-*a*]-pyrimidine in a single step. This compound was then easily converted to the corresponding carboxylic acid **7** by oxidation with potassium permanganate in acidic solution.

In theory, it should be possible to obtain compound **6** from **3** in one step by means of Vilsmeier reaction, because **3** has the electron donating group OH in position 5. However, this reaction gave only 3-formyl-5-hydroxy-7-methyl-2-phenylimidazo[1,2-*a*]pyrimidine **8**, because the hydroxyl group was not replaced by chlorine.

The structures of compounds **3-8** were confirmed by ^{1}H- and ^{13}C-nmr spectral data. As regards the substitution pattern of pyrimidine ring, it should be noted that it depends upon the initial cyclocondensation, which in theory can afford two isomeric products, that is the 5-hydroxy-7-methyl derivative **3** and/or the 7-hydroxy-5-methyl derivative **3a** (Figure 2). The structures of the following compounds **4-7** obviously depend upon the isomer which is obtained in the first synthetic step. The right structure of all compounds was ascertained by nOe experiments performed on product **5**. These experiments showed that the methoxy group is at position 5 and the methyl group at 7.

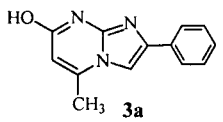


Figure 2

In fact, after irradiation at H-3, a positive nOe effect was observed for the methoxy CH_3, whereas the other methyl group was completely unaffected. On the other hand, the irradiation of the methyl group gave a positive nOe effect only for H-6, whereas H-3 was unaffected. In conclusion, the correct structures of all imidazo[1,2-*a*]pyrimidines prepared are those indicated in Scheme 2.

EXPERIMENTAL

Thin layer chromatography on precoated silica gel plates (Whatman K6F) was used to control the course of reactions and the purity of products. Detection of the components was made by either UV light or by treatment with iodine vapors. Column chromatography was performed on silica gel Merck (70-230 mesh). Melting points were determined with a Kofler hot stage microscope and are uncorrected. The ^{1}H-, ^{13}C- and nOe nmr spectra were recorded on a Bruker AMX 500 spectrometer with chemical shift values reported in δ (ppm) relative to tetramethylsilane as the internal standard.

5-Hydroxy-7-methyl-2-phenylimidazo[1,2-*a*]pyrimidine (**3**).

To a solution of 32 g (0.25 mole) of 2-*a*mino-4-hydroxy-6-methylpyrimidine (**1**) in 250 ml of dimethylformamide was added 2-bromoacetophenone (**2**, 20 g, 0.1 mole) and the reaction mixture was stirred and refluxed for 3 hours. After cooling, the crystallized product was filtered and dried *in vacuo* to give 17.8 g (80%) of **3**, mp 315-317°; ^{1}H nmr (dimethylsulfoxide-d_6): δ 2.47 (s, 3H, 7-CH_3), 5.81 (s, 1H, 6-H), 7.50 (m, 1H), 7.58 (m, 2H) and 8.09 (dd, 2H) (phenyl protons), 8.22 (s, 1H, 3-H).

Anal. Calcd. for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66. Found: C, 69.30; H, 4.88; N, 18.62.

5-Chloro-7-methyl-2-phenylimidazo[1,2-*a*]pyrimidine (**4**).

A solution of 14 g (0.06 mole) of product **3** in 200 ml of phosphorus oxychloride was stirred and refluxed for 2.5 hours. The reaction solution was then cooled, diluted with water and basified with 3*N* sodium hydroxide aqueous solution until *p*H 8 obtaining a precipitate which was collected, air-dried and recrystallized from *n*-hexane to yield 5.8 g (40%) of **4**, mp 173-175°; ^{1}H nmr (deuteriochloroform): δ 2.62 (s, 3H, 7-CH_3), 6.82 (s, 1H, 6-H), 7.87 (s, 1H, 3-H), 7.36 (m, 1H), 7.42 (m, 2H) and 8.02 (dd, 2H) (phenyl protons); ^{13}C nmr (deuteriochloroform): δ 24.7 (7-CH_3), 104.2 (6-CH), 108.9 (3-CH), 128.6, 128.5 (phenyl CH), 132.8 (2-C), 134.7 (phenyl C), 146.9 (5-C), 149.1 (8a-C), 159.3 (7-C).

Anal. Calcd. for $C_{13}H_{10}ClN_3$: C, 64.20; H, 4.94; N, 17.28. Found: C, 64.18, H, 4.91; N, 17.26.

5-Methoxy-7-methyl-2-phenylimidazo[1,2-*a*]pyrimidine (**5**).

A mixture of 5.7 g (0.02 mole) of product **4** and sodium methoxide solution (1 g of sodium in 50 ml of anhydrous methanol) was stirred and refluxed for 13 hours. The reacted solution was evaporated to dryness *in vacuo* and the residue was

extracted with chloroform. The organic extract was evaporated to obtain 5.2 g (92%) of **5**, mp 133-135°; ^{1}H nmr (deuteriochloroform): δ 2.48 (s, 3H, 7-CH_3), 3.99 (s, 3H, 5-OCH_3), 5.89 (s, 1H, 6-H), 7.60 (s, 1H, 3-H), 7.32 (m, 1H), 7.34 (m, 2H) and 7.92 (dd, 2H) (phenyl protons); ^{13}C nmr (deuteriochloroform): δ 25.3 (7-CH_3), 56.6 (5-OCH_3), 86.7 (6-CH), 100.9 (3-CH), 126.0, 128.0 and 128.5 (phenyl CH), 133.5 (2-C), 145.4 (5-C), 150.4 (8a-C), 154.6 (phenyl C), 161.6 (7-C).

Anal. Calcd. for $C_{14}H_{13}N_3O$: C, 70.27; H, 5.48; N, 17.56. Found: C, 70.18; H, 5.45; N, 17.51.

5-Chloro-3-formyl-7-methyl-2-phenylimidazo[1,2-*a*]pyrimidine (**6**).

To a stirred solution of 11ml of phosphorus oxychloride, 32 ml of chloroform and 8 ml of dimethylformamide, mantained at 10°, was added slowly a solution of 5g (0.02 mole) of product **5** in 140 ml of chloroform. The mixture so obtained was refluxed for 4.5 hours. After cooling, the solution was evaporated to dryness *in vacuo*. The residue was treated with water and filtered to obtain 3.4 g (62%) of product **6**, mp 156-158°; ^{1}H nmr (dimethylsulfoxide-d_6): δ 2.34 (s, 3H, 7-CH_3), 5.88 (s, 1H, 6-H), 7.48 (m, 2H) and 8.09 (m, 3H) (phenyl protons), 10.83 (s, 1H, formyl proton); ^{13}C nmr (dimethylsolfoxide-d_6): δ 18.2 (7-CH_3), 97.9 (6-CH), 122.6 (3-C), 127.6, 129.2 and 129.5 (phenyl CH), 132.0 (2-C), 145.2 (5-C), 148.3 (8a-C), 151.3 (phenyl C), 159.1 (7-C), 180.2 (CHO).

Anal. Calcd. for $C_{14}H_{10}ClN_3O$: C, 61.89; H, 3.71; N, 15.46. Found: C, 61.95; H, 3.65; N, 15.50.

5-Chloro-7-methyl-2-phenylimidazo[1,2-*a*]pyrimidine-3-carboxylic acid (**7**).

To a solution of 3 g (0.01 mole) of product **6** in 2*N* sulphuric acid were added slowly 20 ml of an aqueous solution of potassium permanganate (1.6 g, 0.01 mole). The mixture was stirred at room temperature until complete decoloration and then adjusted to *p*H 5 to precipitate the of the acid **7** which was recrystallized from methanol (1.9 g, 66%), mp 164-166°; ^{1}H-nmr (methanol-d_4): δ 3.32 (s, 3H, 7-CH_3), 6.02 (s, 1H, 6-H), 8.27 (m, 1H) and 8.93 (dd, 4H) (phenyl protons).

Anal. Calcd. for $C_{14}H_{10}ClN_3O_2$: C, 58.44; H, 3.50; N, 14.60. Found: C, 58.48, H, 3.55; N, 14.55.

3-Formyl-5-hydroxy-7-methyl-2-phenylimidazo[1,2-*a*]-pyrimidine (**8**).

To a stirred solution of 11ml of phosphorus oxychloride, 32 ml of chloroform and 8 ml of dimethylformamide, mantained at 10°, was added slowly a solution of 4.8g (0.02 mole) of product **3** in 140 ml of chloroform. The mixture so obtained was refluxed for 4.5 hours. After cooling, the solution was evaporated to dryness *in vacuo*. The residue was treated with water and filtered to obtain 1.5 g (30%) of product **8**, mp >200° dec.; ^{1}H nmr(dimethylsulfoxide-d_6): δ 2.42 (s, 3H, 7-CH_3), 5.96 (s, 1H, 6-H), 7.57 (m, 2H) and 8.17 (m, 3H) (phenyl protons), 10.92 (s, 1H, formyl proton); ^{13}C nmr (dimethylsolfoxide-d_6): δ 19.0 (7-CH_3), 98.6 (6-CH), 128.2, 128.4 and 129.9 (phenyl CH), 130.1 (3-C), 132.7 (2-C), 145.9 (5-C), 148.5 (8a-C), 151.7 (phenyl C), 159.7 (7-C), 180.9 (CHO).

Anal. Calcd. for $C_{14}H_{11}N_3O_2$: C, 69.32; H, 4.92; N, 18.66. Found: C, 69.29; H, 4.95; N, 18.63.

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