Synthesis of 7-Substituted Imidazo[1,2-*a*]pyrimidin-5(1*H*)-ones

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The synthesis of 7-substituted imidazo[1,2-*a*]pyrimidin-5(1*H*)-ones by either of 2 methods is reported.

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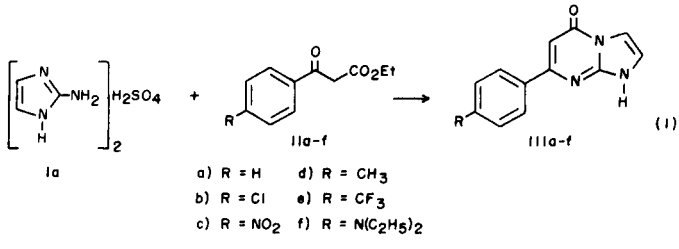
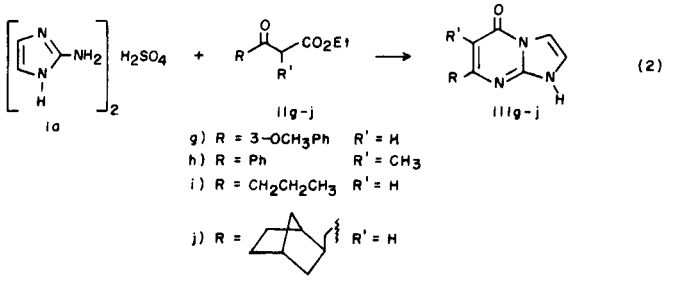
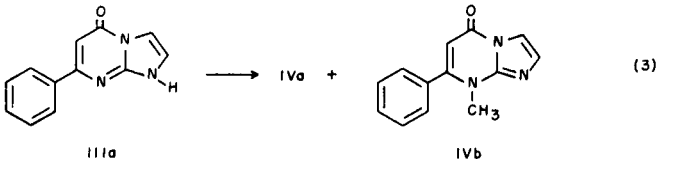
There are many synthetic approaches to imidazo[1,2-*a*]-pyrimidines and 2,7-disubstituted imidazo[1,2-*a*]pyrimidin-5-ones [1], but only a few examples of the synthesis of 7-monosubstituted imidazo[1,2-*a*]pyrimidin-5(1*H*)-ones [2]. In pursuing these compounds, we have examined two routes which involve the condensation of 2-aminoimidazole sulfate (Ia) [3] and β-keto esters under either acidic or basic conditions.

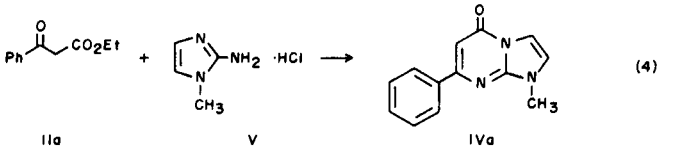
Method A.

Ethyl benzoyl acetate (IIa) and Ia were heated together in PPA at 130° for 1 hour, and then, while still hot, the viscous, green reaction mixture was poured onto ice/water. The precipitate was collected by filtration, then recrystallized from ethanol to yield the analytically pure 7-phenylimidazo[1,2-*a*]pyrimidin-5(1*H*)-one (IIIa) in 49% yield. This reaction was then applied to other aryl β-keto esters IIb-f (equation 1) which were prepared from the appropriate benzoyl chloride and monoethyl malonate [4] or more conveniently on a small scale from the benzoic acid by conversion to the acetophenone with methyl lithium then condensation with ethyl carbonate [5]. These β-keto esters were then treated as above, and the crude imidazopyrimidinones recrystallized from ethanol or DMF/water to give analytically pure products IIIb-f. As can be seen from Table 1, the reactions all proceed with a great deal of success for these 4-substituted phenyl derivatives.









Surprisingly, this procedure was not as useful when applied to other phenyl derivatives. Specifically, ethyl (3-methoxybenzoyl)acetate (IIg) and ethyl 2-benzoylpropionate (IIh) did not yield any product when subjected to the standard conditions. In these cases we turned to a procedure which employed basic reaction conditions.

Method B.

Ethyl (3-methoxybenzoyl)acetate (IIg), 2-aminoimidazole sulfate (Ia) and powdered sodium hydroxide were mixed in a Petri dish with a small volume of dry ethanol and left to stand for 24 hours [6]. The yellow, gummy residue was then placed in a vacuum desiccator over concentrated sulfuric acid for 24 hours, whereupon the acid was replaced by a fresh amount, and the reaction allowed to proceed for an additional 24 hours. The residue was diluted with water, the precipitate collected, and recrystallized from ethanol to give pure IIIg. This method was then expanded to include IIh and alkyl β-keto esters IIi,j as shown in equation 2. We found it best to run this reaction as described over a drying agent, although we did not study the use of other desiccants.

We confirmed the isomeric structure of these condensation products by preparing both *N*-methyl derivatives of IIIa. Methylation of IIIa with iodomethane and potassium carbonate in methanol gave a mixture of the two *N*-methyl isomers IVa and IVb, which could be easily separated by chromatography (equation 3). The major isomer (86% of the crude mixture) was identified as 1-methyl-7-phenylimidazo[1,2-*a*]pyrimidin-5(1*H*)-one (IIIa) by comparison with an authentic sample prepared from 1-methyl-2-aminoimidazole hydrochloride (V) [3] (equation 4). Additional study showed that the nmr of IVa was nearly identical to that of

Table 1

Compound No.	Method	Yield (%)	Mp (°C) (Solvent)	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIIa	A	49	300-302 (EtOH)	68.23	4.29	19.89	67.85	4.31	19.53
	B	25							
IIIb	A	56	181-183 (EtOH)	58.67	3.28	17.10	58.31	3.19	16.87
IIIc	A	63	>330 (DMF/H_2O)	56.25	3.15	21.87	56.15	3.27	21.49
IIId	A	42	188-190 (DMF/H_2O)	69.32	4.92	18.66	69.06	4.88	18.41
IIIe	A	30	292 (EtOH)	55.92	2.89	15.05	55.91	3.11	14.77
IIIf	A	41	267-267.5 (EtOH)	68.06	6.42	19.84	67.94	6.47	19.76
IIIg	B	14	256-257 (CH_3CN)	64.72	4.60	17.42	64.64	4.76	17.44
IIIh	B	10	245 (i-PrOH/H_2O)	69.32	4.92	18.66	69.03	5.11	18.28
IIIi	B	13	131-132 (CH_3CN)	61.00	6.26	23.71	60.97	6.37	23.71
IIIj	B	15	212-213.5 (i-PrOH)	69.11	7.04	17.27	68.71	7.18	17.08

Table 2

Compound No.	UV (95% ethanol)/λ (ε)
IIIa	247 (35,250), 273 (16,000), 288 sh (10,100), 321 (7,550)
IVa	249 (32,650), 276 (15,950), 290 sh (10,000), 325 (7,950)
IVb	212 sh (19,000), 233 (25,400), 259 sh (7,950), 269 sh (6,100), 307 (7,050)
IIIi	219 (27,500), 248 (4,300), 294 (10,050)

IIIa, especially with regard to the C-6 proton. In both examples, the proton was observed to resonate at 6.3-6.4 ppm, while this proton appeared at 5.7 ppm in IVb. This difference is due to the change in the aromatic character of the pyrimidinone ring between the different isomeric forms. As illustrated in Table 2, the uv spectra of IIIa and IVa absorption patterns are essentially identical and completely dissimilar with respect to IVb. We were thus gratified to see that our original assignment of the (1H) structure to the condensation was correct. In the work of Guerret [2] a similar condensation between 2-aminoimidazole hydrochloride (Ib) and IIa in acetic acid/ethanol was reported to give the (8H) isomer. We were unable to affect the condensation of Ia and IIa under the conditions given by Guerret and were thus unable to compare the products.

Through comparison of the uv spectra of IIIa and IIIi (Table 2), we were confident that no structural isomerism had occurred upon changing the method of condensation or the nature of C-7 substituent. The differences that are present in the two spectra are simply due to the contribution from the C-7 substituent and not from changes in the nature of the imidazopyrimidine ring [2].

These two methods are quite useful for the preparation of imidazo[1,2-*a*]pyrimidin-5(1*H*)-ones. For many cases the PPA induced condensation gave good yields of the fused heterocycle, but in those cases where it failed, the sodium hydroxide route did give some product, even if the yield was rather poor.

EXPERIMENTAL

Mass spectra, infrared spectra, ultraviolet spectra, and combustion analysis were obtained by the Physical and Analytical Chemistry Department of The Upjohn Company. Proton nmr spectra (90 MHz) were recorded on a Varian EM-390 instrument with tetramethylsilane as the internal standard. Melting points were measured on a Thomas-Hoover apparatus and are uncorrected.

Table 3

Compound No.	IR (cm^{-1})	^{1}H-NMR (δ ppm) [a]	MS m/e
IIIa	1660	8.0 (m, 2H), 7.4 (m, 5H), 6.3 (s, 1H)	211 (M), 183, 170, 155, 129
IIIb	1676, 1594	8.1 (d, J = 8, 2H), 7.5 (m, 4H), 6.5 (s, 1H)	245 (M), 217, 182
IIIc	1675, 1600	7.8 (m, 2H), 7.6 (d, J = 2, 1H), 7.5 (d, J = 2, 1H), 7.3 (m, 2H), 6.5 (s, 1H)	256 (M), 228, 182
IIId	1668, 1602	7.9 (d, J = 8, 2H), 7.55 (d, J = 2, 1H), 7.5 (d, J = 2, 1H), 7.25 (d, J = 8, 2H), 6.3 (s, 1H), 2.3 (s, 3H)	225 (M), 197, 182, 143
IIIe	1663, 1568, 1554	8.2 (d, J = 9, 2H), 7.8 (d, J = 9, 2H), 7.6 (d, J = 2, 1H), 7.5 (d, J = 2, 1H), 6.5 (s, 1H)	279 (M), 251, 197, 170, 151
IIIf	1661, 1599	8.1 (d, J = 8, 2H), 7.6 (d, J = 2, 1H), 7.5 (d, J = 2, 1H), 7.2 (d, J = 8, 1H), 6.4 (s, 1H), 3.6 (q, J = 7, 4H), 1.1 (t, J = 7, 6H)	282 (M), 267, 239, 210
IIIg	1652, 1588	7.8 (d, J = 2, 1H), 7.7 (d, J = 2, 1H), 7.3 (m, 4H), 6.6 (s, 1H), 3.9 (s, 3H)	241 (M), 212, 183
IIIh	1673	7.6 (d, J = 2, 1H), 7.45 (m, 6H), 2.0 (s, 3H)	225 (M), 196, 115
IIIi	1685, 1613	7.7 (d, J = 2, 1H), 7.1 (d, J = 2, 1H), 5.75 (s, 1H), 2.65 (t, J = 7, 2H), 1.8 (m, 2H), 1.1 (t, J = 7, 3H)	177 (M), 162, 149, 121
IIIj	1673, 1643	7.5 (d, J = 2, 1H), 7.35 (d, J = 2, 1H), 5.65 (s, 1H), 2.6-1.0 (m, 13H)	243 (M), 215, 149, 121, 95

[a] Solvent: DMSO-d_6, except IIIc,g trifluoroacetic acid and IIIi deuteriochloroform.

Method A.

7-Phenylimidazo[1,2-*a*]pyrimidin-5(1*H*)-one (IIIa).

2-Aminoimidazole sulfate (Ia) (4.0 g, 15.1 mmoles), ethyl benzoylacetate (IIa) (5.8 ml, 33.5 mmoles) and PPA (20 g) were heated to 130° for 1 hour, then while still hot poured onto ice/water (50 ml). After stirring for 15 minutes, the precipitate was collected by filtration and recrystallized from ethanol: 3.14 g (14.9 mmoles, 44%), mp 300-302°.

Method B.

7-(3'-Methoxyphenyl)imidazo[1,2-*a*]pyrimidin-5(1*H*)-one (IIIg).

Ethyl (3-methoxybenzoyl)acetate (IIg) (5.40 g, 24.3 mmoles), 2-aminoimidazole sulfate (Ia) (3.21 g, 12.1 mmoles), and absolute ethanol (0.7 ml) were mixed in a crystallizing dish with powdered sodium hydroxide (0.97 g, 24.3 mmoels) and absolute ethanol (1.0 ml). The mixture was loosely covered with a watch glass and occasionally stirred over a 24 hour period. The crystallizing dish was then transfered to a desiccator and left to stand over concentrated sulfuric acid for 24 hours. The desiccant was then replaced with fresh sulfuric acid and the reaction left for an additional 24 hours. The thick paste was then diluted with water (50 ml) and the resulting precipitate collected by filtration. Crystallization from acetonitrile and Darco yielded an off-white solid, 0.82 g (3.4 mmoles, 14%), mp 256-257°.

Methylation of 7-Phenylimidazo[1,2-*a*]pyrimidin-5(1*H*)-one.

Compound IIIa (1.00 g, 4.7 mmoles) in dry methanol (25 ml) was treated with potassium carbonate (750 mg, 5.4 mmoles) and iodomethane (0.44 ml, 7.1 mmoles), then refluxed for 18 hours. After cooling to 22°, the reaction was concentrated *in vacuo*, and the residue stirred with chloroform then filtered through magnesium sulfate. Evaporation of the solvent left a brown solid (1.21 g) which was chromatographed on silica gel with chloroform eluant. The first species isolated was identified as 8-methyl-7-phenylimidazo[1,2-*a*]pyrimidin-5(8*H*)-one (IVb), 14 mg (0.062 mmoles, 1.3%) mp 176.5-178°; nmr (deuteriochloroform): δ 7.7 (d, J = 2, 1H), 7.5 (m, 5H), 7.2 (d, J = 2, 1H), 5.8 (s, 1H), 3.7 (s, 3H); nmr (DMSO-d_6): δ 7.7 (d, J = 2, 1H), 7.55 (m, 5H), 7.3 (d, J = 2, 1H), 5.7 (s, 1H), 3.6 (s, 3H).

The primary spot was then isolated and after recrystallization from methylene chloride/hexane, it was identified as 1-methyl-7-phenylimidazo[1,2-*a*]pyrimidin-5(1*H*)-one (IVa); 535 mg (2.37 mmoles, 51%), mp 113-115°; nmr (deuteriochloroform): δ 8.0 (m, 2H), 7.55 (d, J = 3, 1H), 7.4 (m, 3H), 6.9 (d, J = 3, 1H), 6.5 (s, 1H), 3.7 (s, 3H); nmr (DMSO-d_6): δ 8.1 (m, 2H), 7.45 (m, 5H), 6.4 (s, 1H), 3.7 (s, 3H).

Anal. Calcd. for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66. Found: C, 68.94; H, 4.86; N, 18.40.

1-Methyl-7-phenylimidazo[1,2-*a*]pyrimidin-5(1*H*)-one (IVa).

2-Amino-1-methylimidazole hydrochloride (V) (1.50 g, 11.2 mmoles), ethyl benzoylacetate (IIa) (2.27 g, 11.8 mmoles), and PPA (6 g) were stirred at 120° for 3 hours, then poured onto ice/water. The precipitate was collected by filtration, then recrystallized from ethanol, 0.78 g, mp 206-207°. The crude crystals were placed in a Soxhlet extractor and washed with chloroform for 3 days. After removal of the solvent, 0.35 g (1.55 mmoles, 14%) mp 116-117° was obtained; nmr (deuteriochloroform): δ 8.0 (m, 2H), 7.55 (d, J = 3, 1H), 7.4 (m, 3H), 6.9 (d, J = 3, 1H), 6.5 (s, 1H), 3.7 (s, 3H).

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