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4-Amino-2-arylpyrimidines can be prepared conveniently by the reaction of an amidine with the readily available 3-ethoxyacrylonitrile, 2-chloroacrylonitrile or 2-(1-piperidinylmethyl)acrylonitrile.

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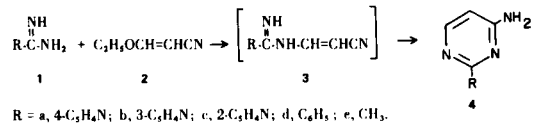
In our work we had a need for 2-aryl-4-aminopyrimidines (**4**). The preparation of this type of compound is usually a multistep process: amidine (**1**) → 4-hydroxypyrimidine → 4-chloropyrimidine → 4-aminopyrimidine (**4**). In a search for a shorter path to these compounds we have found three useful processes that have a potentially broader utility.

We first noted Tarsio and Nicholl's (1) base catalyzed condensation of 3-ethoxyacrylonitrile (**2**) with urea to give cytosine. We have found that 3-ethoxyacrylonitrile (2) reacts with amidines (**1**) to give excellent yields of 4-aminopyrimidines (**4**) (Method A, Table I). No basic catalyst is needed. A slight disadvantage of this process

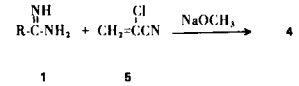


R = a, 4-C_5H_4N; b, 3-C_5H_4N; c, 2-C_5H_4N; d, C_6H_5; e, CH_3.

Method A

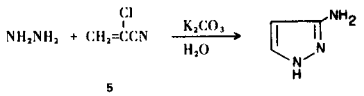
is that two steps are required to prepare the 3-ethoxyacrylonitrile (**2**) (1).

After some further exploration, we found that the readily available 2-chloroacrylonitrile (**5**) also reacts with amidines (**1**) to give 4-aminopyrimidines (**4**) (Method B, Table I). Here a basic catalyst is required: we used sodium methoxide in methanol at room temperature. In

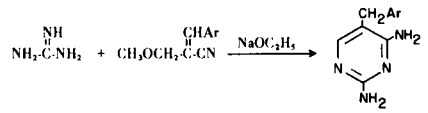


Method B

a limited study of this sequence, we obtained lower yields than with Method A, except for **4a** (Table I). After we had finished this, a related reaction of 2-chloroacrylonitrile (**5**) was reported by Ege and Arnold (2).

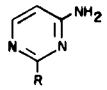


Another novel 4-aminopyrimidine synthesis was used to prepare **4f** (Method C). 2-(1-Piperidinylmethyl)-acrylonitrile (**6**), easily prepared by a modified Mannich reaction on cyanoacetic acid (3), gave on warming with



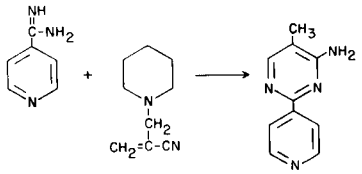
amidine **1a** a 67% yield of **4f**. The nearest example to this type of sequence that we could find was that reported by Stenbuck, *et al.*, (4). The mechanisms for these two processes obviously have several possible pathways and without further evidence deserve no comment.

Table I



Compound No.	R	Yield % Method A	Yield % Method B	M.p. °C	Nmr (a) H-5 (δ)	Nmr (a) H-6 (δ)	J (Hz)
4a	4-C_5H_4N	73	70	262-264 (b)	7.15	8.36	7.5
4b	3-C_5H_4N	80	34	157-159	7.12	8.32	7.5
4c	2-C_5H_4N	60	17	(c)	7.18	8.43	7.5
4d	C_6H_5	77	39	(d)	6.92	8.17	7.5
4e	CH_3	50	15	204-206 (e)	6.96	8.06	8.0

(a) In deuteriotrifluoroacetic acid-TMS. (b) Melting point of the dihydrochloride-hydrate salt, 199° dec. (c) Melting point of the dimethanesulfonic acid salt, 184-186°. (d) Polymorphic: melted at 120°, resolidified and melted at 138-140°. Lit. (5) reports melting at 125°, resolidification and melting at 138-138°. (e) Lit. (6). m.p. 205°.



None of these three relatively novel syntheses have been explored adequately to define the substituent effects or optimum reaction conditions but do hold the promise of broader utility for the preparation of some useful 4-aminopyrimidines.

EXPERIMENTAL

The nmr spectra were obtained on a Varian HA-100 spectrometer. Melting points are uncorrected. Acetamidine hydrochloride and benzamidine hydrochloride were obtained from Aldrich Chemical Co. and 3-ethoxyacrylonitrile (**2**) from Kay-Fries Chemicals, Inc.

The 2- (**1c**) and 3-pyridinecarboxamidine hydrochlorides (**1b**) were prepared by the convenient procedure of Schaefer and Peters (7). The preparation of the 4-isomer (**1a**) by this procedure is described here.

4-Pyridinecarboxamidine Hydrochlride (**1a**).

A solution of 370 g. (3.55 moles) of 4-pyridinecarbonitrile and 20 g. (0.37 moles) of sodium methoxide in 1.7 l. of dry methanol was stirred at room temperature for 1.5 hours, then 200 g. (3.7 moles) of ammonium chloride was added and stirring continued overnight. The resulting solid was collected and the filtrate was evaporated to dryness. The two crops were combined and recrystallized from water to give 394 g. (70%) of **1a**, m.p. 250-252° dec., lit. (8), m.p. 242-244°.

Anal. Calcd. for $C_6H_8ClN_3$: Cl, 22.49. Found: 22.61.

4-Amino-2-(4-pyridinyl)pyrimidine (**4a**).

Method A.

A mixture of 157.8 g. (1.0 mole) of 4-pyridinecarboxamidine hydrochloride (**1a**), 54.2 (1.0 mole) of sodium methoxide in 400 ml. of dry methanol was stirred for 30 minutes. The sodium chloride was collected and the filtrate was concentrated to dryness. The residue thus obtained and 97.9 g. (1.0 mole) of 3-ethoxyacrylonitrile (**2**) were heated (100-160°) together for 3 hours, at this point the evolution of ethanol had stopped and the melt had started to crystallize. After the product had cooled to room temperature, it was slurried in methanol, filtered and dried, 125.6 g. (73%), m.p. 262-264°.

Anal. Calcd. for $C_9H_8N_4$: C, 62.78; H, 4.68; N, 32.54. Found: C, 62.64; H, 4.60; N, 32.28.

Method B.

A mixture of 15.8 g. (0.1 mole) of 4-pyridinecarboxamidine hydrochloride (**1a**) and 5.4 g. (0.1 mole) of sodium methoxide in 75 ml. of dry methanol was stirred for 20 minutes. With continued stirring, 8.9 g. (0.1 mole) of 2-chloroacrylonitrile (**5**) was added over 15 minutes and then 5.4 g. (0.1 mole) more of sodium methoxide in 25 ml. of methanol was added over 40 minutes. After further stirring for 3 hours, the reaction mixture was evaporated to dryness. The resulting solid was washed well with water and then with ethanol and dried, giving 12.1 g. (70%) of **4a**, m.p. 262-264°. The products from this and from Method A were shown to be identical by nmr and by mixed melting point.

Compounds **4b**, **4c**, **4d** and **4e** were also prepared by both Methods A and B (Table I).

4-Amino-2-(3-pyridinyl)pyrimidine (**4b**).

Anal. Calcd. for $C_9H_8N_4$: C, 62.78; H, 4.68; N, 32.54. Found: C, 62.57; H, 4.67; N, 32.18.

4-Amino-2-(2-pyridinyl)pyrimidine (**4c**).

This compound was characterized as the dimethanesulfonate salt.

Anal. Calcd. for $C_{11}H_{16}N_4O_6S_2$: C, 36.25; H, 4.43; N, 15.38. Found: C, 36.09; H, 4.50; N, 15.34.

4-Amino-5-methyl-2-(4-pyridinyl)pyrimidine (**4f**).

A mixture of 64 g. (0.4 mole) of 4-pyridinecarboxamidine (**1a**), 28.2 g. (0.52 mole) of sodium methoxide and 300 ml. of methanol was stirred for 15 minutes and then 65 g. (0.43 mole) of 2-(1-piperidinylmethyl)acrylonitrile (**6**) (3) was added. The resulting mixture was refluxed for 15 hours and then evaporated to dryness. The residue was washed with water and then recrystallized from ethanol giving 51.4 g. (67%) of **4f**, m.p. 224-226°; nmr (deuteriotrifluoroacetic acid): δ 2.45 (CH_3), 8.31 (H-6).

The dimethanesulfonate salt was prepared as the analytical sample, m.p. 210-213° (from ethanol).

Anal. Calcd. for $C_{12}H_{18}N_4O_6S_2$: C, 38.09; H, 4.79; N, 14.86. Found: C, 37.81; H, 4.81; N, 14.41.

Acknowledgement.

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