Large Scale Synthesis of 4-Ethylpyrimidine

M. Butters

Process Research & Development,
Pfizer Central Research, Ramsgate Road,
Sandwich, Kent, CT13 9NJ, U.K.

Received February 25, 1992

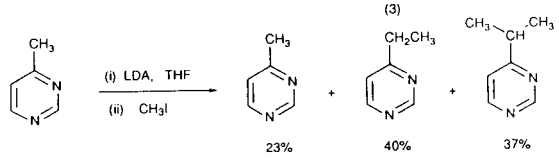
The reaction of methyl propionyl acetate with formamidine acetate in the presence of sodium methoxide produces 6-ethyl-4(3*H*)-pyrimidinone (**1**) in 67% isolated yield. Reaction with phosphorus oxychloride and subsequent catalytic hydrogenolysis affords 4-ethylpyrimidine (**3**) in 41% overall yield.

J. Heterocyclic Chem., **29**, 1369 (1992).

Recently, we wanted to prepare 4-ethylpyrimidine (**3**) in multikilogram quantities. Only two syntheses of 4-ethylpyrimidine (**3**) have previously been reported in the literature [1] [2]. In the first case, Kirillova [1] employed acetylene based starting materials which are hazardous and in short supply. Subsequently, Koyama [2] reported a condensation using methyl ethyl ketone and formamide which gave rise to a mixture of ethyl and dimethyl pyrimidines which were not successfully separated.

Initially, we investigated an approach [3] based upon low temperature alkyl lithium chemistry starting from the commercially available 4-methylpyrimidine [4]. Unfortunately, scale up of this methodology resulted in mixtures of 4-ethyl, 4-isopropyl and 4-methylpyrimidine (Scheme 1) which could not be separated by distillation. Furthermore, severe exotherms were observed (−70° to +10°) during addition of the methyl iodide and consequently this approach was abandoned.

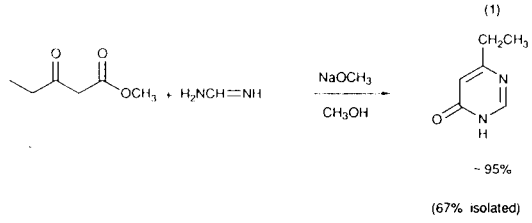
Scheme 1



Formamidine acetate [5] is a versatile building block for pyrimidines and other heterocyclic compounds. One potential route to 4-ethylpyrimidine would involve direct condensation of 1,1-diethoxypentan-3-one (or synthetic equivalents thereof) with formamide. However, in the absence of a commercial source for 1,1-diethoxypentan-3-one, we considered synthesis of the pyrimidine at a higher oxidation state. Thus 6-ethyl-4(3*H*)-pyrimidinone (**1**) was identified as an attractive intermediate.

The reported literature method [6] for the preparation of compound **1** involves treatment of 2,6-dichloro-4-ethylpyrimidine with hydrogen iodide and red phosphorus. In the search for a more efficient method of preparation we found that condensation of formamidine acetate with methyl propionyl acetate [7] (Scheme 2) under anhydrous basic conditions [8] gave a near quantitative yield of 6-ethyl-4(3*H*)-pyrimidinone (**1**). This reaction was highly selective and gave **1** as a white crystalline solid in good yield.

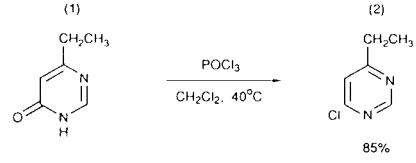
Scheme 2



The desired 4-ethylpyrimidine (**3**) was obtained in two further steps (Scheme 3 and 4) from 6-ethyl-4(3*H*)-pyrimidinone (**1**). Chlorination of **1** using phosphorus oxychloride in refluxing dichloromethane gave 4-chloro-6-ethylpyrimidine (**2**) [6] (Scheme 3). This reaction was complete after 3 hours and gave **2** as a crude oil in 85% yield after workup. The crude oil containing **2** was then successfully hydrogenated in the next step without recourse to further purification.

A number of conditions were evaluated for dechlorination of **2** including ammonium formate/palladium-on-carbon, hydrogen/triethylamine/bis(triphenylphosphine)palladium(II) chloride and hydrogen/aqueous caustic/palladium-on-carbon. However, best results were obtained by catalytic hydrogenolysis in the presence of palladium-on-carbon and sodium acetate (mild base) providing **3** in 73% yield (Scheme 4).

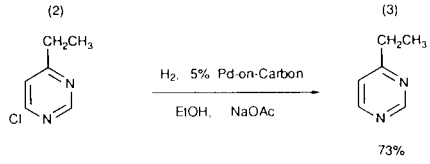
Scheme 3



In summary, the new synthesis of 4-ethylpyrimidine (**3**) has several advantages over previous reported procedures [1-3]. In particular, the chemistry provides ethylpyrimidine free from isomers and homologues and is therefore more efficient in the use of starting materials and obviates the requirement for purification by chromatography or distil-

lation. The overall yield from methylpropionyl acetate was 41% and, moreover, the chemistry has been successfully carried out on a multikilogram scale.

Scheme 4



EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined on a Bruker ACP 300 spectrometer using tetramethylsilane as an internal reference. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet). The mass spectra were determined on a VG7070F spectrometer.

6-Ethyl-4(3*H*)-pyrimidinone (**1**).

Formamidine acetate (83.2 g, 0.80 mole) was added to a solution of sodium methoxide (85.8 g, 1.60 mole) in methanol (700 ml), followed by methyl propionylacetate (83.7 g, 0.64 mole), and the whole reaction was stirred at ambient temperature for four hours. After cooling to 10°, water (440 ml) was added, followed by glacial acetic acid (48.0 g, 0.8 mole). Solvent was removed under vacuum, and water was added. The aqueous was extracted with methyl ethyl ketone (3 x 150 ml), and the combined organics concentrated to low volume. Ethyl acetate (85 ml) was added, with cooling and granulation to produce 53 g (67%) of **1** after filtration and drying. An analytical sample was recrystallised from ethyl acetate, mp 127-129°; ^{1}H nmr (DMSO-d_6): δ 1.1 (t, 3H), 2.4 (q, 2H), 6.1 (s, 1H), 8.1 (s, 1H); ms: m/z 124 (molecular ion).

4-Chloro-6-ethylpyrimidine (**2**).

A mixture of **1** (50.0 g, 0.4 moles) in methylene chloride (250 ml) was heated to reflux and phosphorus oxychloride (77.2 g, 0.504 mole) was added portionwise over one hour. After 3 hours reaction time, the mixture was cooled to 30° before quenching into cold water (200 ml) over 30 minutes. The *p*H of the quench was adjusted to *p*H 4 using 0.880 sp gr ammonia (150 ml), before separating the two phases. The aqueous phase was washed with methylene chloride (200 ml), and the combined organics were backwashed with brine (200 ml). Removal of solvent afforded 48.8 g (85%) of **2**, bp 193° (atmospheric pressure); ^{1}H nmr (deuteriochloroform): δ 1.1 (t, 3H), 2.65 (q, 2H), 7.1 (s, 1H), 8.75 (s, 1H); ms: m/z 142 (molecular ion).

4-Ethylpyrimidine (**3**).

To a solution of **2** (20.0 g, 0.14 mole) in industrial methylated spirit (100 ml) was added sodium acetate (12.0 g, 0.146 mole) and 5% palladium on carbon (50% wet) (5.0 g), and the resulting slurry was hydrogenated at 50° and 50 psi for 3 hours. Catalyst was removed by filtration through arbacel filter aid, and the filtrate was concentrated under vacuum. The residue was partitioned between methylene chloride (75 ml) and water (75 ml), and the *p*H was adjusted to *p*H 8 using 40% aqueous sodium hydroxide. The two phases were separated and the aqueous phase was washed further with methylene chloride (75 ml). The combined organics were backwashed with brine (75 ml) before removal of solvent to produce 11.0 g (73%) of **3**, bp 140° (atmospheric pressure); ^{1}H nmr (deuteriochloroform): δ 1.2 (t, 3H), 2.65 (q, 2H), 7.05 (d, 1H), 8.45 (d, 1H), 9.0 (s, 1H); ms: m/z 108 (molecular ion).

Acknowledgement.

The author wishes to thank Arthur Bentley, Mike Reader and Dave Dale for their technical input.

REFERENCES AND NOTES

[1] M. A. Kirillova, *Zh. Org. Khim.*, **6**, 1528 and 2374 (1970).

[2] T. Koyama, T. Hirota, C. Bashou, Y. Satoh, Y. Watanabe, S. Matsumoto, Y. Shinohara, S. Ohmori and M. Yamato, *Chem. Pharm. Bull.*, **23**, 2158 (1975).

[3] Private communication with K. Dack, Pfizer Central Research, Sandwich, Kent.

[4] H. Bredereck, *Org. Synth.*, **43**, 77. Also available from Lancaster Synthesis, U.K.

[5] E. C. Taylor and W. A. Ehrhart, *J. Am. Chem. Soc.*, **82**, 3138 (1960).

[6] W. T. Caldwell and W. M. Ziegler, *J. Am. Chem. Soc.*, **58**, 78 (1936).

[7] Available in bulk from Lonza.

[8] C. Luthy, EP 114045 (1984) (to Hoffmann-La Roche).