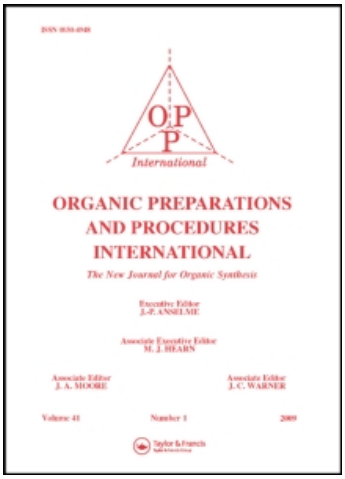

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LARGE SCALE SYNTHESIS OF 2-CHLORO-5-FLUOROPYRIMIDINE

Audrey Dunaiskis[a]; Tom Staigers[a]; Tom Keltonic[a]; Tom Chappie[a]; Cliff Meltz[a]; Robert Dugger[a]; Mark A. Sanner[a]

[a] Departments of Process Development, Process Research and Medicinal Chemistry, Pfizer Central Research, Groton, CT

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5. B. P. Cho, *Org. Prep. Proced. Int.*, **27**, 243 (1995).

6. M. W. Chou, R. H. Heflich, D. A. Casciano, D. W. Miller, J. F. Freeman, F. E. Evans and P. P. Fu, *J. Med. Chem.*, **27**, 1156 (1984).

7. R. G. Harvey and P. P. Fu, *Org. Prep. Proced. Int.*, **14**, 414 (1982).

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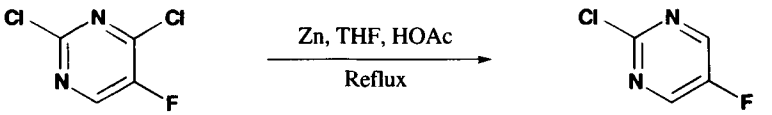
LARGE SCALE SYNTHESIS OF 2-CHLORO-5-FLUOROPYRIMIDINE

Submitted by (12/05/94) Audrey Dunaiskis, Tom Staigers, Tom Keltonic, Tom Chappie, Cliff Meltz, Robert Dugger and Mark A. Sanner*

Departments of Process Development, Process Research and Medicinal Chemistry Pfizer Central Research, Groton, CT 06340

The introduction of 2-amino-5-fluoropyrimidine functionality, found in neuroleptics such as the sigma receptor ligand BMY-14802,[1,2] is accomplished with derivatives of 5-fluorouracil such as 2,4-dichloro-5-fluoropyrimidine (**1**) and 2-chloro-5-fluoropyrimidine (**2**). Synthesis of 2-amino analogs from **1** requires initial protection of the 4-position with sulfur followed by later removal with Raney nickel; the regioselective protection is consistent with the preference for nucleophilic attack at the 4-chloro position.[1,3] Derivative **2** is available by a variation of the sulfur/Ra-Ni strategy,[4] or by hydrogenolysis of 2,4,6-trichloro-5-fluoropyrimidine.[5] While these methods are acceptable for preparing gram-quantities of **2** and its 2-amino derivatives, we required a method suitable for kilogram-scale synthesis.



1 **2**

Our investigation focused on a three-phase dechlorination of **1** using zinc in aqueous ammonium hydroxide and benzene.[6] A modification of this procedure with granular zinc and one mole equivalent of acetic acid in refluxing THF proved to be extremely useful for preparing as much as 1000 g of **2** in 55-65% yield. Granular zinc is preferred over more active forms such as zinc dust because the reaction rate can be difficult to control with zinc dust, especially when it is activated by

acid washing. The reaction rate also seems to depend on the age and source of the zinc, with older lots being less reactive. Moreover, we have observed an induction period for the reaction if all the acetic acid is added at room temperature before reflux begins. On the other hand, the reaction proceeds smoothly and predictably if the acetic acid is added slowly to a refluxing mixture of granular zinc and dichloride **1** in THF.

We have developed a new kilogram-scale synthesis of **2** by dechlorination of **1** with Zn/HOAc/THF in 55-65% yield. The ready availability of **2** by this method will greatly facilitate the preparation of a wide variety of biologically active 2-amino-5-fluoropyrimidines.

EXPERIMENTAL SECTION

NMR spectra were recorded in $CDCl_3$ on a Brüker AM300 spectrometer at 300MHz and are reported in ppm downfield from internal TMS. Boiling points are uncorrected.

2-Chloro-5-fluoropyrimidine (2).- A 22 L round bottom flask equipped with a mechanical stirrer, thermocouple, reflux condenser, and 1000 mL addition funnel was charged with 10 L of THF, 2.00 kg (12.0 moles) of 2,4-dichloro-5-fluoropyrimidine (**1**)[7] and 2.35 kg (35.9 moles) of zinc granules (-10+50 mesh). ***[Caution! Zinc powder, especially when activated by acid washing, may react vigorously and is not recommended].*** The mixture was heated to reflux with vigorous stirring, and 686 mL (12.0 moles) of glacial acetic acid was added *via* the addition funnel over a 1 h period ***[Caution! Adding the acetic acid at room temperature and heating to reflux may exhibit an induction period followed by a sudden exotherm].*** The mixture refluxed until <1% **1** remained by HPLC (usually about 5 hrs). The mixture was cooled to 40°, poured into a solution of 4.8 kg of ethylenediaminetetraacetic acid tetrasodium salt in 5 L of water, and stirred at room temperature overnight. Supercel (200 g) was added and the mixture filtered through Supercel; the filter cake was washed with ethyl acetate. The filtrate was diluted with 10 L of ethyl acetate, the mixture was stirred for 30 min, the layers were separated, the aqueous phase was extracted twice with 5 L and then 2.5 L of ethyl acetate and the combined organic phase was filtered through Supercel. Fractional distillation through a 120 x 45 cm column packed with Hasteloy® springs gave 0.873-1.03 kg (55-65%) of 2-chloro-5-fluoropyrimidine, bp 149-162°, lit.[5] 92-94°/100 mbar which was ≥ 97% pure by HPLC. HPLC conditions: Zorbax RX-C8 column (4.6 x 150 mm); mobile phase: 1200 mL water, 800 mL acetonitrile, 3 mL phosphoric acid, 6 mL triethylamine; 1 mL/min flow rate; 210 nm UV detection. Retention times: 2,4-dichloro-5-fluoropyrimidine = 24.6 min, 2-chloro-5-fluoropyrimidine = 6.2 min. ^1H NMR ($CDCl_3$): δ 8.51 (s). ^{13}C NMR ($CDCl_3$): δ 147.4 (C-H, J_{CF} = 22 Hz), 155.6 (C-Cl, J_{CF} = 2.5 Hz), 157.1 (C-F, J_{CF} = 265 Hz).

REFERENCES

1. J. P. Yevich, J. S. New, W. G. Lobeck, P. Dextraze, E. Bernstein, D. P. Taylor, F. D. Yocca, M. S. Eiso and D. L. Temple, Jr., *J. Med. Chem.*, **52**, 4515 (1992); R. Foguet Ambròse, S. Gubert

Ribera, C. Braojos Fabra, J. A. Oritz Hernandez, J. M. Castellò Barenys and A. Sacristan Muñoz, *ES2030634* (1991); *Chem. Abstr.*, **118**, 254962a (1992).

2. C. J. Ohnmacht, Y. K. Yee, D. A. Trainor and J. J. Lewis, *EP532178 A1* (1993); *Chem. Abstr.*, **119**, 271004 (1993).

3. V. Uchytilovià, A. Holy, D. Cech and J. Gut, *Czech. Chem. Commun.*, **40**, 2347 (1975), ; T. Ueda and J. J. Fox, *J. Med. Chem.*, **6**, 697 (1963).

4. M. Gacek, *Acta Chem. Scand. B*, **39**, 691 (1985).

5. B. Baasner and E. Klauke, *J. Fluorine Chem.*, **45**, 417 (1989).

6. D. J. Brown and T.-C. Lee, *Australian J. Chem.*, **21**, 243 (1968); D. J. Brown and P. Waring, *ibid.*, **26**, 243 (1973).

7. Interchem Corp., 120 Route 17 N, Suite 115, Paramus, NJ 07662