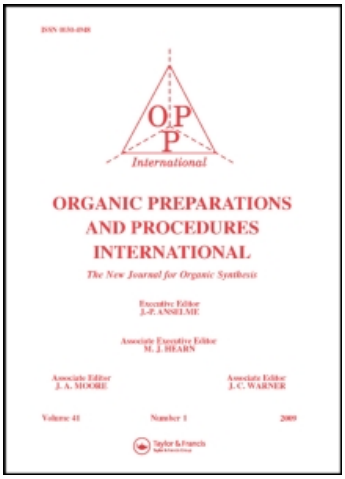


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

A CONVENIENT SYNTHESIS OF METHYL 4-AMINO-5-CHLORO-2-MTHOXYBENZOATE

Richard L. Ehrenkaufer[a]; James G. Scripko[ab]; Patricia L. Hoffman[a]
[a] University of Pennsylvania PET Center/Cyclotron Facility, Philadelphia, PA [b] Parke-Davis Pharmaceutical Research Division, Ann Arbor, MI

To cite this Article Ehrenkaufer, Richard L. , Scripko, James G. and Hoffman, Patricia L.(1992) 'A CONVENIENT SYNTHESIS OF METHYL 4-AMINO-5-CHLORO-2-MTHOXYBENZOATE', Organic Preparations and Procedures International, 24: 1, 64 — 66
To link to this Article: DOI: 10.1080/00304949209356701
URL: http://dx.doi.org/10.1080/00304949209356701

A CONVENIENT SYNTHESIS OF METHYL 4-AMINO-5-CHLORO-2-METHOXYBENZOATE

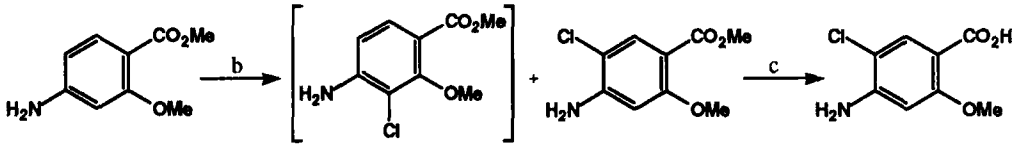
Submitted by (08/05/91)

Richard L. Ehrenkaufer*, James G. Scripko† and Patricia L. Hoffman

University of Pennsylvania PET Center/Cyclotron Facility
429 Johnson Pavilion, 6th & Hamilton Walk
Philadelphia, PA 19104

A common feature of many neuroleptic drugs available on the market today is the 4-amino-5-chloro-2-methoxybenzoic acid moiety.[1,2] During a program of synthesizing a number of these drugs and their radiolabelled analogues for evaluation as potential Positron Emission Tomography imaging agents, we needed to develop a convenient synthesis of the parent acid. Published syntheses involved protection-deprotection of the nitrogen,[3] to prevent overoxidation by molecular chlorine or the use of iodobenzene dichloride,[4] a reagent no longer readily available from commercial sources and which must be synthesized. Both methods have another drawback, namely the required handling of chlorine gas. We report here a synthesis of this acid using N-chlorosuccinimide (NCS) as the selective chlorinating agent.[5]

Our synthesis starts with the inexpensive 4-aminosalicylic acid which was methylated with Me_2SO_4/KOH according to the method of Murakami[4] to give methyl 4-amino-2-methoxybenzoate (**1**). This material can be either purified *via* recrystallization from ethyl acetate/hexanes or used directly in the next step without purification. Chlorination of **1** with a slight molar excess of NCS in refluxing acetonitrile gave methyl 4-amino-5-chloro-2-methoxybenzoate (**2b**) contaminated with 15% of the regioisomer methyl 4-amino-3-chloro-2-methoxybenzoate (**2a**).[6] Again, this material can be purified by recrystallization from methanol or hydrolyzed directly. Saponification under standard conditions followed by a single recrystallization from methanol gave acid **3** of greater than 99% purity.[7]



1 **2a** **2b** **3**

(a) N-chlorosuccinimide, MeCN, 94%; (b) KOH, H_2O; HCl, 86%.

This synthesis takes advantage of the ability of NCS in acetonitrile to chlorinate aniline derivatives under extremely mild conditions.[8] Among the advantages of NCS *vs.* Cl_2 gas for laboratory scale reaction are ease of handling, stability, ready availability and modest cost. Combining these features with the reaction's tolerance of varying conditions as well as the simple workup involved make this sequence a useful method for synthesizing the title acid in 10-100 g quantities.

EXPERIMENTAL SECTION

All reagents and starting materials were obtained from Aldrich Chemical and were used as received. NMR spectra were taken on a Varian EM360 Spectrometer with $CDCl_3$ as solvent and tetramethylsilane as the internal standard. HPLC analyses were done on a Varian 5500 using a normal-phase silica column and eluting with a mixture of 70% MeCN and 30% 0.004M $(NH_4)_2HPO_4$.

Methyl 4-Amino-5-chloro-2-methoxybenzoate (2b).- Methyl 4-amino-2-methoxybenzoate[4] (29.51 g, 0.163 mol) was dissolved in 250 ml of MeCN in a round bottomed flask equipped with a reflux condenser and a magnetic stirring bar. N-chlorosuccinimide (22.83 g, 0.171 mol) was added in one portion and the mixture refluxed for 1 hr. After cooling, the solvent was removed on a rotary evaporator and the solid residue was then suspended in 10% $NaHSO_3$(aq) and stirred for 1.5 hr.The precipitated crystals were collected and washed repeatedly with water (5 x 100 mL). After air drying overnight, a mixture of **2a** and **2b** as light brown crystals (33.06 g, 94%). Analysis of the crude mixture by HPLC showed only two materials present in an 85:15 ratio. NMR analysis of the crude product also showed the two isomeric chlorination products in a 6:1 ratio, identifiable by the signals from the aromatic protons. These two compounds could be separated by column chromatography (silica gel, 1:1 EtOAc/hexanes), or **2b** could be isolated in pure form by recrystallization from MeOH (4 ml per gram of crude material, 87% yield of **2b**). The latter method gave methyl 4-amino-5-chloro-2-methoxybenzoate as off-white crystals (26.11 g, 0.121 mol, 74%), mp. 134-136°, lit.[1] mp. 135-137°. NMR of **2b:** δ 3.55 (s, 3), 3.60 (s, 3), 4.65 (br s, 2), 5.75 (d, 1, J = 10 Hz), 7.15 (d, 1, J = 10 Hz); NMR of **2a**: δ 3.50 (s, 3), 3.55 (s, 3), 4.70 (br s, 2), 6.05 (s, 1), 7.30 (s, 1).

Acknowledgements.- This work supported by NIH Grants NS 14867 and MH 43880.

REFERENCES

† Current address: Parke-Davis Pharmaceutical Research Division, 2800 Plymouth Road, Ann Arbor, MI 48106.

1. J. Prieto, J. Moragues, R. G. Spickett, A. Vega, M. Columbo, W. Salazar and D. J. Roberts, *J. Pharm. Pharmac.*, **29**, 147 (1977).

2. P. N. C. Elliot, P. Jenner, G. Huizing, C. D. Marsden and R. Miller, *Neuropharm.*, **16**, 333 (1977); F. Brown, W. Campbell, M. S. G. Clark, D. S. Graves, M. S. Hadley, J. Hatcher, P. Mitchell, P. Needham, G. Riley and J. Semple, *Psychopharm.*, **94**, 350 (1988); T. Hoberg. P.Strom, T. de Paulis, B. Stensland, J. Csoregh, K. Lund, H. Hall and S.O. Ogren, *J. Med. Chem.*, **34**, 948 (1991).

3. M. L. Thiomet, Fr. Patent 1,476,925 (1967); *Chem Abs.*, **68**, 95562a (1967).

4. M. Murakami, N. Inukai, A. Koda and K. Nakano, *Chem. Pharm. Bull. Japan*, **19**, 1696 (1971).

5. R. S. Neale, R. G. Schepers and M. R. Walsh, *J. Org. Chem.*, **29**, 3390 (1964).

6. This ratio was determined by the integration of the appropriate peaks in the aromatic region of the nmr spectrum of the crude reaction mixture. It was confirmed by HPLC analysis of the crude mixture.

7. Purity determined by HPLC.

8. T. E. Nickson and C. A. Roche-Dolson, *Synthesis*, 669 (**1985**).

****

IMPROVED SYNTHESIS OF DIMETHYLAMINOTHIOACETAMIDE

Submitted by (08/29/91) Kenneth P. Moder*, Frank R. Busch and David C. Richter

Lilly Research Laboratories
Eli Lilly and Co., Lafayette, IN 47902

Aminothioamides are useful starting materials in the synthesis of pharmaceutical agents such as, N-alkyl-N'-([2-(aminoalkyl)-4-thiazolylmethyllthioalkyl)guanidines, thioureas, and ethanediamine anti-ulcer agents.[1] Thiation of amides with various phosphorus reagents has been reviewed.[2] However, aminothioamides generally are prepared by reaction of hydrogen sulfide with an aminoamide in the presence of an amine such as ammonia, pyridine, or triethylamine. Vasil'eva's work illustrates this process with the preparation of dimethylaminothioacetamide in 56% non-isolated yield.[3] Unfortunately, the amine often interferes with the isolation of the desired product. If the amine base is removed by distillation, lower yields of the aminothioacetamide product result because of co-distillation of amine and product. If the amine is not distilled and the aminothioacetamide is isolated as its acid salt, the final product is highly impure due to co-precipitation of the acid salt of the amine.The problems encountered with homogeneous amines can be overcome by employing alkali metal sulfide salts such as sodium sulfide or sodium hydrosulfide. These salts may be used in anhydrous or hydrated form but the anhydrous or monohydrate forms are preferred. The alkali metal sulfide or hydrosulfide are used in catalytic amounts, 0.5 to 8.0% on a molar basis.

We now report an efficient process for the synthesis of dimethylaminothioacetamide hydrochloride from the corresponding dimethylaminoacetonitrile, hydrogen sulfide, and sodium sulfide. This method obviates the need for amines and solvent exchanges employed previously and