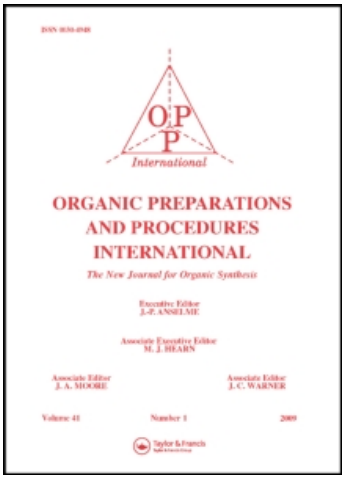


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

PREPARATION OF 4-CHLORO-2-THIOPHENECARBOXYLIC ACID *via* SELECTIVE BISULFITE SALT ADDITION PROCEDURE

Jeffrey W. Raggon[a]; Jennifer M. Welborn[a]; Jane E. Godlewski[a]; Sarah E. Kelly[a]; Thomas G. Lacour[a]
[a] Central Research Division, Pfizer Inc. Process Research and Development, Groton, CT

To cite this Article Raggon, Jeffrey W. , Welborn, Jennifer M. , Godlewski, Jane E. , Kelly, Sarah E. and Lacour, Thomas G.(1995) 'PREPARATION OF 4-CHLORO-2-THIOPHENECARBOXYLIC ACID *via* SELECTIVE BISULFITE SALT ADDITION PROCEDURE', Organic Preparations and Procedures International, 27: 2, 233 — 236
To link to this Article: DOI: 10.1080/00304949509458460
URL: http://dx.doi.org/10.1080/00304949509458460

PREPARATION OF 4-CHLORO-2-THIOPHENECARBOXYLIC ACID *via* SELECTIVE BISULFITE SALT ADDITION PROCEDURE

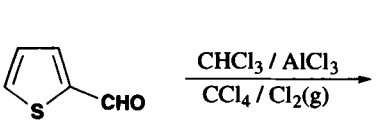
Submitted by (03/18/94)

Jeffrey W. Raggon*, Jennifer M. Welborn, Jane E. Godlewski, Sarah E. Kelly and Thomas G. LaCour

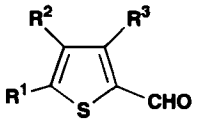
Central Research Division, Pfizer Inc.
Process Research and Development
Groton, CT 06340

A key reaction in a proposed synthesis of 4-chloro-2-thiophenecarboxylic acid **6** is the regioselective chlorination of 2-thiophene-carboxaldehyde **1**. The chlorination of **1** in the presence of excess $AlCl_3$ to give **6** has been reported.[1] However, the product was separated from the undesired positional chloro isomers by column chromatography. Herein we would like to report a more general method of isolating **6** that is amenable to large-scale preparation. Purification of aldehydes from mixtures as the bisulfite salt is well documented.[2] There are, however, few examples where closely related aldehydes are separated by selective formation and precipitation of one addition product in preference to the other.[3] This communication reports on such an example, whereby a mixture of the mono- and dichlorothiophene aldehydes are separated as their bisulfite adducts followed by conversion of the desired adduct converted to the title compound.

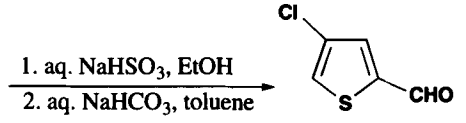
The synthesis began by the reaction of a mixture of excess $AlCl_3$ and **1** in $CHCl_3$ with Cl_2 in CCl_4 at 0°. The resulting mixture of starting material **1**, 4-chloro-2-thiophenecarboxaldehyde (**2**), 5-chloro-2-thiophene-carboxaldehyde (**3**) and 4,5- and 3,4-dichloro-2-thiophenecarboxaldehyde (**4**) and (**5**)[4] was diluted with ethanol and added to an aqueous solution of 4.8 M $NaHSO_3$ and stirred for 16 hrs at ambient temperature. The bisulfite adduct was isolated in 83% yield. The purified aldehyde **2** was obtained by adding the salt to an aqueous solution of 1 M $NaHCO_3$ and toluene.[5] The biphasic



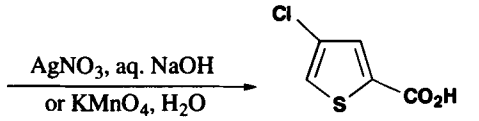
1



2, $R^1 = R^3 = H$; $R^2 = Cl$
3, $R^1 = Cl$; $R^2 = R^3 = H$
4, $R^1 = R^2 = Cl$; $R^3 = H$
5, $R^1 = H$; $R^2 = R^3 = Cl$



2



6

mixture was stirred for 15 hrs to yield 62% of **2** that was shown by HPLC[6] analysis to be 96% pure. Oxidation of aldehyde **2** to the corresponding acid **6** was accomplished either with Ag_2O (generated *in situ* from $AgNO_3$, aq. NaOH)[1] in 72% yield, or more conveniently, with aqueous $KMnO_4$[7] to afford a 67% yield of **6**. Trituration of **6** in hexane increased its purity to 99% as judged by HPLC.

EXPERIMENTAL SECTION

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were recorded on a Brucker 300 MHz spectrometer in $CDCl_3$ unless noted otherwise. Mass spectra were obtained with a Hewlett-Packard 5890 GC using a HP-1 12m capillary column in tandem with a HP model 5971 mass selective detector. High Resolution mass spectra were recorded on a Kratos Profile instrument at 70 ev. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory. 2-Thiophene-carboxaldehyde **1** was purchased from Lancaster. All reagents were used as received without purification.

4-Chloro-2-thiophenecarboxaldehyde (2) and Thiophene Aldehydes (1, 3-5).- A 1 L round-bottomed flask was charged with 600 mL of CCl_4 and cooled to 10°. Cl_2 (39.5 g, 0.558 mol) was then slowly bubbled into the CCl_4, maintaining a slow agitation rate and a temperature of 10°. A 3 L round-bottomed flask was charged with 500 mL of $CHCl_3$ and 2-thiophene-carboxaldehyde (50 g, 0.446 mol), and cooled to 0°. To this dark amber aldehyde solution was charged $AlCl_3$ (133.8 g, 1.0 mol) in portions, maintaining the reaction temperature at <5° throughout the addition. The Cl_2/CCl_4 solution previously prepared was then added to this mixture as rapidly as possible. The temperature of the resulting amber slurry was increased to 20° and the mixture was stirred for 14 hrs. The reaction mixture was quenched by slow addition to 1 L of aq. 6N HCl solution (previously cooled to 10°) contained in a 5 L round-bottomed flask; the quenching process was exothermic and the temperature was maintained at <20° throughout by controlling the addition rate. When the addition was complete, the mixture was stirred for 1 hr at ambient temperature, and the layers were allowed to separate. The organic layer was removed, and the aqueous layer was extracted with 1 L of $CHCl_3$. The organic layers were combined, washed with 1 L of H_2O, and concentrated to dryness to yield 100.0 g of a crude dark amber oil. ^1H NMR: **2**, δ 9.82 (d, 1H), 7.60 (d, 1H), 7.50 (d, 1H); **1**, δ 9.92 (m, 1H), 7.76 (m, 2H), 7.20 (m, 1H); **3**, δ 9.73 (d, 1H), 7.70 (d, 1H), 7.05 (d, 1H); **4**, δ 10.0 (d, 1H), 7.55 (d, 1H); **5**, δ 10.03 (d, 1H), 7.60 (d, 1H). GCMS (EI) m/e: **2**, 146 (M^+), 148 (M+2); **1**, 112 (M^+); **3**, 146 (M^+), 148 (M+2); **4**, 180 (M^+), 182 (M+2), 184 (M+4); **5**, 180 (M^+), 182 (M+2), 184 (M+4).

Bisulfite Addition Product of 4-Chloro-2-thiophenecarboxaldehyde.- A 1 L round-bottomed flask was charged with 42.5 mL of H_2O and $NaHSO_3$ (21.23 g, 0.204 mol). To this solution cooled to 10°, was added a solution of 20 g of the crude aldehyde mixture (assumed 0.116 mol, 100%) in 140 mL of EtOH over 20 min. The temperature throughout the addition was maintained at 10-15°. When the addition was complete, the reaction temperature was allowed to become ambient and stirred for 16 hrs, whereupon a light brown slurry had formed. The solids were collected and washed with 2x40 mL of EtOH. The wet cake was dried under vacuum at 50° for 24 hrs to yield 24.1 g (83%) of a tan solid,

mp. >245°. ^{1}H NMR (DMSO-d_6): δ 7.38 (d, 1H), 7.02 (d, 1H), 6.58 (d, 1H), 5.17 (d, 1H).

4-Chloro-2-thiophenecarboxaldehyde (2).- A 1 L round-bottomed flask was charged with 465 mL of H_2O and $NaHCO_3$ (41.9 g, 0.499 mol). To this solution was added the bisulfite addition product obtained above (25 g, 0.10 mol). The brown mixture was stirred at ambient temperature for 15 min and then 375 mL of toluene was added. The biphasic mixture was stirred at ambient temperature for 15 hrs and then allowed to settle for 60 min. After separation of the layers, the organic phase was washed with 100 mL of H_2O. The combined aqueous layers were then stirred with 375 mL of toluene for 2 hrs. The layers were separated and the two organic phases were combined and washed with 188 mL of H_2O. After separation, the organic layer was concentrated *in vacuo* to yield 9.1 g (62%) of a dark amber oil. ^{1}H NMR: δ 9.82 (d, 1H), 7.60 (d, 1H), 7.50 (d, 1H). IR (neat): 1674, 1414, 1224 cm^{-1}.

Anal. Calcd. for C_5H_3ClOS: C, 40.96; H, 2.06; Cl, 24.18; S, 21.87

Found: C, 40.72; H, 2.13; Cl, 23.84; S, 21.81

HRMS Calcd. for C_5H_3ClOS: 145.9593. Found: 145.9598.

4-Chloro-2-thiophenecarboxylic Acid (6).- A 2 L round-bottomed flask was charged with aldehyde **2** (20.0 g, 0.136 mol) and 160 mL of H_2O. The brown biphasic mixture was heated to 60°, and a solution of $KMnO_4$ (30.0 g, 0.190 mol) in 540 mL of H_2O was added over 50 min. The resulting reaction mixture was stirred at 60° for 2 hrs. The pH of the mixture was adjusted to ~10 using 13 mL of a 10% aq. KOH solution. The MnO_2 formed as a by-product was filtered off and washed with 3 x 50 mL of hot H_2O. The amber filtrate was cooled to ambient temperature, and the pH was adjusted to 2 using 11 mL of conc. HCl. The thin white slurry that formed was stirred at 10° for 3 hrs and collected. The off-white solid was washed with 2 x 50 mL of a 0.5 N aq. HCl solution, and dried under vacuum at 50° for 14 hrs to yield 14.74 g (67%) of **6**, mp. 136-139°. An analytical sample was obtained by adding **6** (10.0 g, 0.0615 mol) to 100 mL of hexane and heating to 70° for 60 min. The mixture was cooled slowly to 20° and then stirred for 2 hrs. The solids were collected, washed with 2 x 20 mL of hexane and dried under vacuum at 40° for 2 hrs to yield 8.96 g (90%) of **6** (>98% pure by HPLC analysis), mp. 138-140°. ^{1}H NMR: δ 13.53 (bs, 1H), 7.91 (d, 1H), 7.66 (d, 1H). IR (KBr): 3100, 1681, 1531, 1429 cm^{-1}.

Anal. Calcd. for $C_5H_3ClO_2S$: C, 36.94; H, 1.86; Cl, 21.81; S, 19.72

Found: C, 36.90; H, 1.87; Cl, 21.55; S, 19.91

HRMS Calcd. for $C_5H_3ClO_2S$: 163.9591. Found: 163.9607.

REFERENCES

1. J. Iriarte, E. Martinez, and J. M. Muchowski, *J. Heterocyclic Chem.*, **13**, 393 (1976).

2. Fieser and Fieser, *"Reagents for Organic Synthesis"*, Vol. 1, John Wiley and Sons, Inc., New York, N. Y. (1967) pp.1047-1049.

3. F. J. Urban and B. S. Moore, *J. Heterocyclic Chem.*, **29**, 431 (1992); S. E. Kelly and B. S. Moore, unpublished results.

4. The ratio of starting material, 4-chloro-, 5-chloro- and 4,5-/3,4-dichlorothiophenecarboxaldehyde isomers was determined by HPLC to be 3:90:4:3 (cf. 6); Surprisingly, when the Friedel-Crafts chlorination was carried out in 1,2-dichloroethane the ratio of chlorothiophene aldehydes formed was 17:61:17:5.

5. M. D. Soffer, M. P. Bellwas, H. E. Gellerson, and R. A. Stewart, *"Organic Synthesis"*, N. Rabjohn, Ed., Coll. Vol. 4, John Wiley and Sons, Inc., New York, N. Y. (1963) pp. 903-906.

6. HPLC conditions: Column: silica, 3.9x150mm Waters Nova-Pak®; Mobile Phase: 0.1% THF/hexane; Flow Rate: 1mL/min; Injection volume: 20ul; UV detection @254nm.

7. R. L. Shriner and E. C. Kleiderer, *"Organic Synthesis"*, A. H. Blatt, Ed., Coll. Vol. 2, John Wiley and Sons, Inc., New York, N. Y. (1943) pp. 538-539.

****

A NEW EFFICIENT SYNTHESIS OF 3-AMINO-1-PHENYLPYRROLE

Submitted by (08/03/94)

Frédéric Fabis, Patrick Dallemagne, Sylvain Rault and Max Robba*

Centre d'Etudes et de Recherche sur le Médicament de Normandie
Laboratoire de Chimie Thérapeutique, U.F.R. des Sciences Pharmaceutiques
1, rue Vaubénard, 14032 Caen, FRANCE

Despite the great interest in 3-aminopyrrole derivatives as building blocks in heterocyclic chemistry, access to these compounds remains quite difficult and the methods described fail for large scale. For example, only one synthesis of 3-amino-1-phenylpyrrole (**9**) has been reported;[1] it involves nitration of 1-phenylpyrrole (**2**), separation of the 2- and 3-nitropyrrole isomers, and subsequent hydrogenation of the latter to **9**. The overall yield and spectrometric data were not reported. In the course of our work concerning the synthesis of new pyrrole derivatives of therapeutic interest, we needed reasonable quantities of 3-amino-1-phenylpyrrole (**9**) and we wished to develop a convenient synthesis on a multigram scale. The results of this study are reported herein.

We recently described an efficient synthesis of 1-arylpyrrole-3-carboxaldehydes (**4**) by acidic transposition of their 2-isomers (**3**),[2] and pointed out their importance for the preparation of new β-aminoacids **5** (Scheme 1).[3] 1-Phenylpyrrole-3-carboxaldehyde (**4**), obtained in 93% yield from aniline **1** was then oxidized to the corresponding carboxylic acid **6** in 85% yield, using silver nitrate and sodium hydroxide in refluxing methanol (Scheme 2). The synthesis of **6** had been previously described in 6 steps starting from 2-buten-1,4-diol in 12% yield but without spectral data. [4] Treatment of **6** with thionyl chloride and followed by sodium azide in acetone gave the carboxylic acid azide **7** in quantitative yield. Curtius rearrangement of **7** in a mixture of dichloroethane and benzyl alcohol