A Convenient Synthesis of the Thieno[3,2-*c*]pyridine Nucleus

James H. Wikel*, Michael L. Denney and Robert T. Vasileff

Lilly Research Laboratories, Eli Lilly and Company,
Indianapolis, Indiana 46285 USA

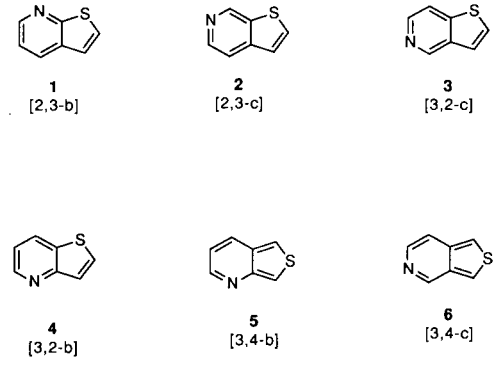
Received September 9, 1992

The unsubstituted thieno[3,2-*c*]pyridine ring system was prepared from thiophene-3-carboxaldehyde in 4 steps. The sequence is suitable for scale-up.

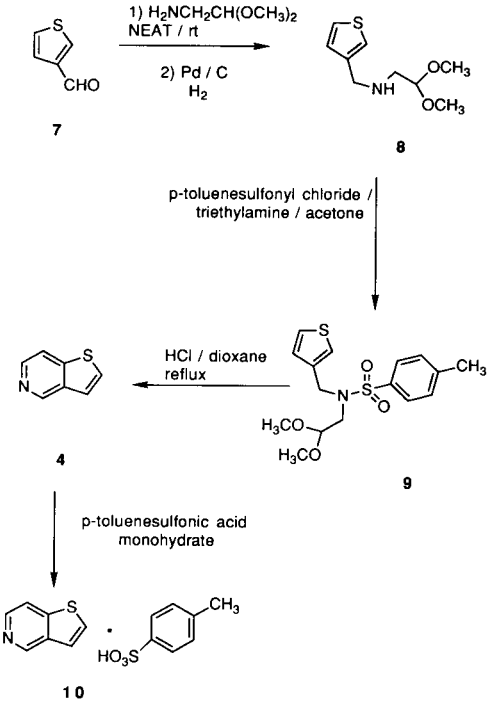
J. Heterocyclic Chem., **30**, 289 (1993).

The thieno[x,y-z]pyridine ring system has been known in the literature for nearly 80 years. The synthesis of thieno-[2,3-*b*]pyridine was reported in 1913 [1,2] and represents only one of six possible isomers **1-6**. All of the isomers have been prepared with varying degrees of success. Their chemistry has been the subject of two reviews [3,4]. The chemistry of the series has been of interest both experimentally and theoretically since the system contains a π-excess and a π-deficient heterocyclic ring. We had an interest in the preparation of these compounds as intermediates and therefore required a suitable laboratory synthesis that would yield reasonable quantities of the heterocycles. Our interest focused on the thieno[3,2-*c*]pyridine isomer. Owing to the similarity of the thieno[x,y-z]pyridines with quinoline and isoquinoline, the synthetic approaches were similar. Examination of the literature revealed that unsubstituted thieno[3,2-*c*]pyridine was obtained from three routes. Herz and Tsai [5] reported a Pomeranz-Fritsch reaction involving the acid induced cyclization of a Schiff base of 3-thiophenecarboxaldehyde and aminoacetaldehyde diethyl acetal. The overall yield was reported at approximately 3.5%. A Picket-Spengler reaction was used by Growowitz and Sandberg [6] by cyclization and subsequent oxidation of the formimine of β-(2-thienyl)ethylamine. Eloy and Deryckere [7] reported a seven step sequence producing the thienopyridine by a cyclization of β-thienylvinyl isocyanate. In 1976 Maffrand and Eloy [8] tersely described a modification of the Herz and Tsai procedure for the preparation of the thieno[3,2-*c*]pyridine as a potentially useful intermediate in the synthesis of an inhibitor of platelet aggregation, ticlopidine. The absence of reported experimental details has prompted us to describe here the preparation with full experimental details of the thieno[3,2-*c*]pyridine nucleus in a sequence of four steps that is suitable for scale up in a laboratory setting.

Thiophene-3-carboxaldehyde **7** and aminoacetaldehyde dimethylacetal were stirred neat at room temperature for 16 hours to form the Schiff base **8**. The Schiff base was reduced under catalytic conditions and then immediately reacted with *p*-toluenesulfonic acid in the presence of triethylamine to yield **9**. The reduction using sodium borohydride was previously reported by Maffrand and Eloy but we found the catalytic method more convenient and yielded a cleaner product [8]. Under these conditions we obtained the product **9** as an oil which slowly crystallizes upon standing at room temperature. Substitution of the



Scheme 1



dimethylacetal with the diethylacetal in the reaction was less desirable since the product did not crystallize and thus was difficult to purify. The desired heterocycle **4** was produced by heating **9** to reflux in dioxane with concentrated hydrochloric acid. The free base of the heterocycle was isolated from the reaction mixture as an oil which slowly crystalized and may be further purified by sublimination. We found the preferred method was isolation of the product as the *p*-toluenesulfonic acid salt **10**. The free base has a low vapor pressure and slowly sublimes at room temperature that results in a characteristic odor we found mildly irritating to the eyes. Isolation of salt is not only quick and easy but does not allow the product to sublime thus eliminating any potential hazard. This is particularly important in storing large quantities of the compound. The above procedure has been successfully performed within one week to yield 100 gram amounts of the thieno-[3,2-*c*]pyridine.

EXPERIMENTAL

N-(2,2-Dimethoxyethyl)-4-methyl-*N*-3-(thienylmethyl)benzenesulfonamide (**9**).

A 1 liter flask was charged with 3-thiophenecarboxaldehyde (224 g, 2 mole) and placed in a ice/water cooling bath. To this was added, with stirring, aminoacetaldehyde dimethylacetal (275 g, 2.6 moles) while maintaining a temperature between 20-25°. The mixture was allowed to stir at ambient temperature for 16 hours. The solution was diluted with ethanol and hydrogenated at 60 psi in the presence of 5% Pallidum on carbon (115.6 g) for 12 hours.

The catalyst was removed by filtration and washed with solvent. The solvent was concentrated *in vacuo* to afford **8** as an oil, yield 383 g (95%). The oil was dissolved in 1 liter of ethyl acetate and cooled to 15° with a cooling bath. To this solution was added triethylamine (170 g, 1.68 moles) with stirring, followed by *p*-toluenesulfonyl chloride (320 g, 1.68 moles) in portions with stirring while maintaining the temperature at 15-20°. After the addition was complete, the reaction was allowed to stir at ambient temperature for 12 hours. The reaction was diluted with ethyl acetate, transferred to a separatory funnel and washed several times with water, 1*N* hydrochloric acid and a dilute sodium carbonate solution. The ethyl acetate was dried with anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo* to yield **9** as a solid, yield 540 g (91% based upon *p*-toluenesulfonyl chloride). The product is sufficiently pure for the cyclization step but was recrystallized from isopropanol for analytical purposes, mp 67-69°; ^{1}H nmr (deuteriochloroform): δ 2.40 (s, 3 H, phenyl-CH_3), 3.23 (d, 2 H, CH_2), 3.30 (s, 6 H, OCH_3), 4.36 (t, 1 H, J = 2 Hz, CH), 6.85 (d, 1 H, J = 4 Hz, thiophene-4-H), 7.05 (d, 1 H, J = 2 Hz, thiophene-2-H), 7.2 (dd, 1 H, J = 4, 2, thiophene-5-H), 7.28 (d, 2 H, J = 5 Hz, phenyl-H), 7.70 (d, 2 H, J = 5 Hz, phenyl-H).

Anal. Calcd. for $C_{16}H_{21}NO_4S_2$: C, 54.06; H, 5.95; N, 3.94. Found: C, 53.96; H, 5.66; N, 3.84.

Thieno[3,2-*c*]pyridine (**4**).

The sulfonamide **9** (540 g, 1.5 moles) was dissolved in dioxane (1500 ml) and stirred while concentrated hydrochloric acid was added (780 ml). The addition was mildly exothermic to approximately 30°. The reaction was heated to a gentle reflux for 16 hours. The dark reaction mixture was then cooled to room temperature and concentrated to approximately one-half volume under vacuum. The reaction solution was washed several times with methylene chloride until the organic washings were colorless. The aqueous layer was basified with ammonium hydroxide and extracted several times with methylene chloride. The organic washings were combined, dried with magnesium sulfate, and evaporated *in vacuo* to yield **4** as an oil, yield 100 g (49%).

Thieno[3,2-*c*]pyridine *p*-Toluenesulfonate Salt (**10**).

To a stirred solution of **4** (100 g, 0.74 mole) in dry acetone (250 ml) was added a solution of *p*-toluenesulfonic acid monohydrate (120 g, 0.63 mole) in dry acetone (300 ml). The mixture was stirred at room temperature for 2 hours, the solid was collected by filtration, and washed with cold acetone to yield **10** as a solid, yield 165.1 g (85% based upon *p*-toluenesulfonic acid monohydrate), mp 136-138°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.29 (s, 3 H, *p*-toluenesulfonic acid CH_3), 7.12 (d, 2 H, J = 7.9, *p*-toluenesulfonic acid aromatics), 7.50 (d, 2 H, J = 7.9, *p*-toluenesulfonic acid aromatics), 7.96 (d, 1 H, J = 5.5, thienopyridine 3-H), 8.36 (d, 1 H, J = 5.5, thienopyridine 2-H), 8.70 (d, 1 H, J = 6.4 Hz, thienopyridine 7-H), 8.79 (d, 1 H, J = 6.4, thienopyridine 6-H), 9.60 (s, 1 H, thienopyridine 4-H).

Anal. Calcd. for $C_{14}H_{13}NO_3S_2$: C, 54.70; H, 4.26; N, 4.56. Found: C, 54.93; H, 4.36; N, 4.44.

REFERENCES AND NOTES

[1] W. Steinkopf and G. Lutzkendorf, *Liebigs Ann. Chem.*, **403**, 45 (1913).

[2] W. Steinkopf and G. Lutzkendorf, *Chem. Ztg.*, **36**, 379 (1913).

[3] S. W. Schneller, *Int. J. Sulphur Chem.*, **7**, 309 (1972).

[4] J. Barker, in Advances in Heterocyclic Chemistry, Vol **21**, A. R. Katritzky and A. Boulton, eds, Academic Press, New York, NY, 1977, pp 65-118.

[5] W. Herz and L. Tsai, *J. Am. Chem. Soc.*, **75**, 5122 (1953).

[6] S. Gronowitz and E. Sandberg, *Arkiv Kemi*, **32**, 217 (1970).

[7] F. Eloy and A. Deryckere, *Bull. Soc. Chim. Belg.*, **79**, 301 (1970).

[8] J. Maffrand and F. Eloy, *J. Heterocyclic Chem.*, **13**, 1347 (1976).