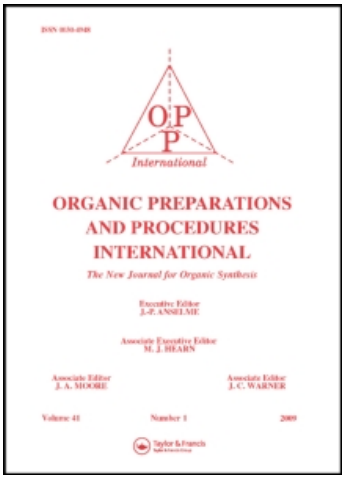


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

AN EFFICIENT PREPARATION OF 2*H*-[5,4-b]-PYRIDOISOTHIAZOLONE

Stephen W. Wright[a]; Ronald L. Corbett[a]
[a] The Du Pont Merck Pharmaceutical Company, Du Pont Experimental Station, Wilmington, DE

To cite this Article Wright, Stephen W. and Corbett, Ronald L.(1993) 'AN EFFICIENT PREPARATION OF 2*H*-[5,4-b]-PYRIDOISOTHIAZOLONE', Organic Preparations and Procedures International, 25: 2, 247 — 249
To link to this Article: DOI: 10.1080/00304949309457957
URL: http://dx.doi.org/10.1080/00304949309457957

AN EFFICIENT PREPARATION OF 2*H*-[5,4-b]-PYRIDOISOTHIAZOLONE

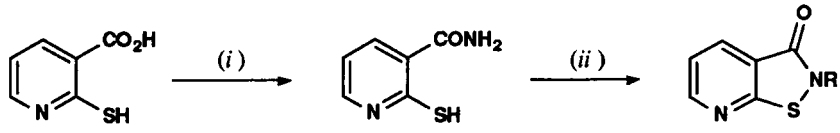
Submitted by (10/22/92)

Stephen W. Wright* and Ronald L. Corbett

The Du Pont Merck Pharmaceutical Company
Du Pont Experimental Station, Wilmington, DE 19880-0353

Pyridoisothiazolones (**1**) have attracted considerable attention as radiosensitizers, antibacterial, antiplatelet, and antifungal agents.[1] 2*H*-[5,4-b]-Pyridoisothiazolone (**1a**) is of particular interest as a starting material for the synthesis of 2-*N* substituted pyridoisothiazolone derivatives.[2] The nucleophilic character of the sulfenamide makes it an attractive intermediate from which a large number of derivatives may be efficiently prepared, in a divergent fashion, by *N*-alkylation and *N*-acylation.[3]

We sought an efficient and convenient method to rapidly prepare multigram quantities of **1a** for use as a synthetic intermediate. However, we found that the preparations of **1a** reported in the literature suffered from several disadvantages, including low overall yields, the use of hydrogen sulfide and/or peracids, inconveniently large reaction volumes, or the use of starting materials that were not commercially available. Herein we report a two-step synthesis (67% overall yield) of **1a** that employs a readily available starting material, inexpensive reagents, and can be easily carried out on a large scale without purification of the intermediate. Our synthesis begins with 2-mercaptonicotinic acid (**2**),[4] which is converted in one flask to 2-mercaptonicotinamide (**3**) by sequential treatment with thionyl chloride, buffered ammonium hydroxide, and sodium borohydride.



2 **3** **1a**, R = H

i) $SOCl_2$, PhMe, reflux;NH_4OH,NH_4Cl;$NaBH_4$. *ii*) H_2SO_4, 100°.

The use of sodium borohydride improves the yield by reducing the disulfide bis-amide present and preventing its disproportionation in the reaction mixture. The 2-mercaptonicotinamide is oxidatively cyclized to the 2*H*-pyridoisothiazolone **1a** by heating with concentrated sulfuric acid, which serves as oxidant and solvent.[5] This avoids the more hazardous use of chlorine, hydrogen peroxide or peracids to effect this transformation.

EXPERIMENTAL SECTION

2-Mercaptonicotinic acid was purchased from Aldrich and Lancaster Synthesis. All other reagents were purchased from J. T. Baker. All reagents were used as received. Reactions were carried out without protection from the atmosphere. Evaporations were carried out on a rotary evaporator using aspirator pressure. Hydrogen chloride evolved in the first step was trapped as described by Vogel.[6]

2-Mercaptonicotinamide (3).- 2-Mercaptonicotinic acid (60 g, 0.38 mol) was suspended in a mixture of toluene (600 mL) and thionyl chloride (180 mL, 1.46 mol) and heated at reflux until a homogeneous solution was obtained (*ca.* 3 hrs.). The mixture was cooled and the acid chloride began to precipitate at once. The mixture was concentrated *in vacuo*, and the residue was suspended in 400 mL of toluene and concentrated again to remove excess thionyl chloride. The crude acid chloride was then added to a mixture of 500 mL (7.50 mol) of conc. NH_4OH, 170 mL of water, and 70 g (1.30 mol) of NH_4Cl. A portion of the NH_4OH/NH_4Cl solution was used to rinse out the flask containing the acid chloride. The mixture was stirred at 20° for 18 hrs., then was treated with 7.56 g (0.20 mol) of $NaBH_4$ added in portions. The mixture was stirred for 1 hr. at 20°, then was acidified with 3 M HCl and the solid was collected to give 43.2 g (73%) of **4**, mp. 245-247°, lit.[3a] 260-262°. ^1H NMR (DMSO-d_6): δ 10.09 (br s, 2 H); 8.49 (d, 1 H); 7.97 (m, 2 H); 7.01 (d, 1 H). MS (NH_3 - CI): *m/z* = 155 (M + H^+). IR (KBr pellet): 3270 - 2800 (s, br, NH and OH); 1672 (s, C=O); 1578 (s, C=C) cm^{-1}. Elemental analysis indicated this material contained approximately 5% elemental sulfur.[7]

2*H*-[5,4-b]-Pyridoisothiazolone (1a).- The product from the first step (**3**, 43.0 g, 0.28 mol) was added with stirring to conc. H_2SO_4 (280 mL, 5.0 mol) and the mixture was immersed in a pre-heated oil bath at 100° until all material had dissolved (ca. 2 hrs). The mixture was then cooled and poured over 700 g of crushed ice. This was made alkaline (pH 11) with 700 mL of concentrated NH_4OH (CAUTION: Heat is evolved!) and a small amount of insoluble matter was removed by filtration. The filtrate was heated to boiling and acidified (pH 4) with glacial AcOH (200 mL) and then allowed to cool. The product was collected, washed with water and dried to give 38.7 g (91%) of **1a**, mp. 234-236°, lit.[1a] 222-224°. ^1H NMR (DMSO-d_6): δ 12.06 (br, 1 H); 8.83 (d, 1 H); 8.32 (d, 1 H); 7.53 (d, 1 H). MS (NH_3 - CI): *m/z* = 153 (M + H^+). IR (KBr pellet): 2700 (m, br, NH and OH); 1674 (s, C=O); 1594 (m C=C) cm^{-1}.

Anal. Calcd for $C_6H_4N_2OS$: C, 47.36; H, 2.65; N, 18.41. Found: C, 46.97; H, 2.43; N, 18.21

REFERENCES

1. See, for example: (a) A. Monge and V. Martinez-Merino, *J. Heterocycl. Chem.*, **25**, 23 (1988); (b)T. Zawisa and W. Malinka, *Acta Pol. Pharm.*, **44**, 32 (1987); (c) J. Maignan and B. Shroot, *U. S. Patent 4,548,942* (22 Oct 1985; *CA* **101**, 116736c); (d) J. L. Rainey and M. C. Seidel, *U. S. Patent 3,965,107* (22 Jun 1976; *CA* **85**;160072h); (e) S.-J. Chang, *U. S. Patent 4,868,310* (19 Sep 1989; *CA* **109**, 128994p).

2. a) J. Maignan and B. Shroot *U. S. Patent 4,512,985* (23 Apr 1985; *CA* **100**, 121052k); b) G. Lang, M. Colin, B. Shroot and J. Maignan *U. S. Patent 4,654,354* (31 Mar 1987; *CA* **105**, 209240j).

3. a) J. Maignan and B. Shroot, *Fr. Demande 83 18721* (24 November 1983; *CA* **101**, 116736c); b) G. Lang, M. Colin, B. Shroot and J. Maignan *US Patent 4,654,354* (31 Mar 1987; *CA* **101**, 116736c)

4. This material typically costs $97-110 per mole. Alternatively, certain literature preparations start with 2-chloronicotinic acid, which costs $115-145 per mole.

5. Sulfuric acid oxidizes the mercaptan to the sulfenic acid according to the following equation:

$$RSH + H_2SO_4 \rightarrow RSOH + SO_2 + 2\,H_2O$$

6. A. Vogel, "*Practical Organic Chemistry*", 4th Edition, p. 61, Longmans, London, 1978.

7. Thionyl chloride oxidizes the mercaptan to the disulfide,[1a] probably according to the following equations:

$$2\,RSH + SOCl_2 \rightarrow RSS(O)SR + 2\,HCl$$

$$RSS(O)SR + RSH \rightarrow RSSR + RSSOH$$

$$RSSOH + RSH \rightarrow RSSR + H_2O + S$$

$$H_2O + SOCl_2 \rightarrow 2\,HCl + SO_2$$

$$\text{Net: } 4\,RSH + 2\,SOCl_2 \rightarrow 2\,RSSR + 4\,HCl + S + SO_2$$

****

AN IMPROVED SYNTHESIS OF

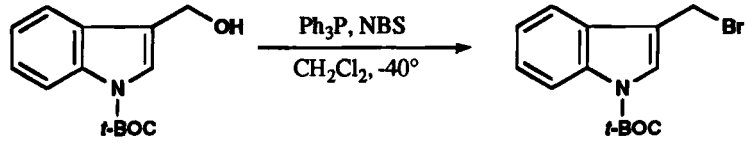
1-(*t*-BUTYLOXYCARBONYL)-3-(BROMOMETHYL)INDOLE

Submitted by (11/16/92)

T. K. Venkatachalam, S. Mzengeza and M. Diksic*

Montreal Neurological Institute, and
Department of Neurology and Neurosurgery
McGill University, 3801 University Street, Montreal, CANADA H3A 2B4

Indolylmethyl bromide **2** has been used in the asymmetric synthesis of α-methyl-L-tryptophan *via* the chiral glycine synthons by Seebach's[1] and Schöllkopf's groups.[2] We have been interested in the asymmetric synthesis of ^{14}C and ^{11}C labelled α-methyl-L-tryptophan.[3] These radiopharmaceuticals are important in the *in vivo* study of the synthesis of the neurotransmitter, serotonin, using both autoradiography[4] and positron emission tomography.[5] Brain serotonin alteration has been implicated in neurological diseases[6] (e. g. schizophrenia, disorders of appetite, mood, sexual behaviour and sleep).[7] All our attempts to prepare indolylmethyl bromide **2** from the corresponding indolylmethyl alcohol **1**



1 **2**