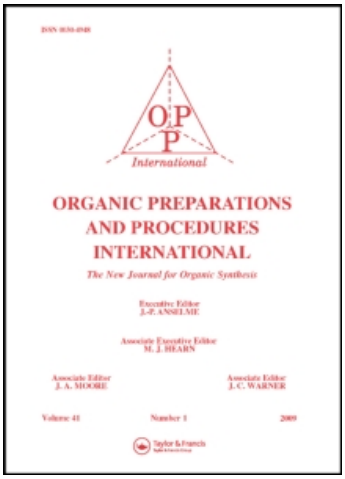


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

A SIMPLE SYNTHESIS OF BRASSILEXIN, A *CRUCIFERAE* PHYTOALEXIN

Michel Devys[a]; Michel Barbier[a]
[a] Institut de Chimie des Substances Naturelles CNRS, Gif-sur-Yvette Cedex, FRANCE

To cite this Article Devys, Michel and Barbier, Michel(1993) 'A SIMPLE SYNTHESIS OF BRASSILEXIN, A *CRUCIFERAE* PHYTOALEXIN', Organic Preparations and Procedures International, 25: 3, 344 — 346
To link to this Article: DOI: 10.1080/00304949309457974
URL: http://dx.doi.org/10.1080/00304949309457974

3. J. Jernow, W. Tautz, P. Rosen and T. H. Williams, *ibid.*, **44**, 4212 (1979).

4. Y. Naoshima, T. Nakayama, H. Kondo, S. Hayashi and H. Ueda, *Agric. Biol. Chem.*, **48**, 1123 (1984).

5. M. L. dos Santos and G. C. de Magalhães, *Synth. Commun.*, **21**, 1783 (1991).

6. E. von Rudloff, *Can. J. Chem.*, **43**, 2660 (1965).

7. Th. J. de Boer and H. J. Backer, *Org. Syn. Coll. Vol. 4*, 250 (1963).

8. R. C. Cookson and S. A. Smith, *J. Chem. Soc., Perkin Trans. 1*, 2447 (1979).

9. J. J. Bloomfield, D. C. Owsley and J. M. Nelke, *Org. Reactions*, **23**, 259 (1976).

10. F. Cooke, G. Roy and P. Magnus, *Organometallics*, **1**, 893 (1982).

****

A SIMPLE SYNTHESIS OF BRASSILEXIN, A *CRUCIFERAE* PHYTOALEXIN

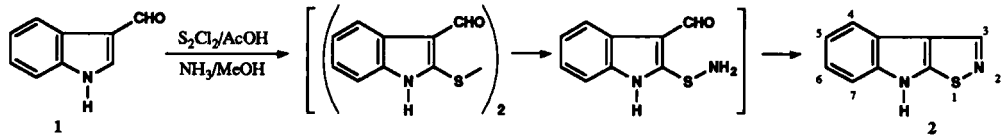
Submitted by (12/08/92)

Michel Devys and Michel Barbier*

Institut de Chimie des Substances Naturelles
CNRS, Avenue de la Terrasse
91198 Gif-sur-Yvette Cedex, FRANCE

Brassilexin (**2**) was previously isolated from plants of the *Cruciferae* family[1,2] together with other sulfur-containing indole-derived phytoalexins.[3] Brassilexin is a powerful anti-fungal compound and is endowed with general cytotoxic properties in human cell cultures.[4] A synthesis of brassilexin (three steps, 11% yield) has been reported previously.[5] It was subsequently demonstrated that the periodate induced oxidation of cyclobrassinin, another Cruciferae phytoalexin, gave brassilexin through a ring contraction of the thiazine moiety.[6a] According to this synthetic scheme, cyclobrassinin monosulfoxide[6b,7] led to a better yield of **2**. Recently, the synthesis of isothiazines through a Lewis acid-promoted attack of the 2-disulfide of a 1-methylketone by ammonia has been reported.[8] According to this report, the resulting sulfenamide easily cyclized to the isothiazole.[9] Thus, the commercially available indole-3-carboxaldehyde **1** was choosen as starting material and converted to the disulfide. The use of BF_3 in methanol in the presence of ammonia triggered the rupture of the disulfide bridge to afford a 30% yield of brassilexin (**2**) in addition to other products. A control experiment, showed that BF_3 was not necessary to the reaction. The prolonged action of ammonia on the disulfide in methanol gave the same yield of **2**. Typically, indole-3-carboxaldehyde (**1**) was heated for a few minutes in a

mixture of S_2Cl_2 and acetic acid. Excess acetic acid was then removed *in vacuo* and methanolic ammonia was added. Brassilexin was isolated from the reaction mixture, purified by repeated TLC on SiO_2 and recrystallized. The physico-chemical properties of **2** were identical to those previously reported for the natural[1] or synthetic[5] product (R_f, mp., UV, MS, high resolution MS and H NMR).



So far it has not been possible to isolate the intermediates of the reaction. It is likely that, due to the excess of sulfur monochloride needed for the reaction, a mixture of polysulfides was also generated. The yields of **2** were poorer when lower amounts of S_2Cl_2 were used. The starting material **1** was quantitatively recovered when an equimolecular amount of S_2Cl_2 was employed. Acetic acid seems to play a role in the protection of the NH group of the indole nucleus since the use of THF as solvent gave a negative result.

EXPERIMENTAL SECTION

Mps were determined on a Kofler apparatus using a microscope and are corrected. The UV spectra were obtained from a Perkin Elmer Lambda-5 automatic spectrophotometer. The MS (electron impact or high resolution) were determined on an AEI MS 50 apparatus and the ^{1}H NMR on a Bruker 300 MHz spectrometer. Schleicher-Schüll SiO_2 fluorescent F_{254} plates (1 mm thick) were used for preparative and analytic TLC.

Isothiazolo[5,4-b]indole 2 (*brassilexin*).- To a solution of indole-3-carboxaldehyde **1** (a Fluka product, 145 mg, 1 mmol) in acetic acid (8 mL) stirred at 60° was added 0.8 mL of sulfur monochloride (S_2Cl_2, 10 mmol). The reaction mixture was kept at 60° for 1 hr and then evaporated to dryness under reduced pressure. Traces of acid were eliminated from the dark brown residue by standing under high vacuo. A solution of NH_3 in absolute methanol (30 mL, saturated at 0°) was added and the mixture was kept at 0° for 1 hr with stirring. It was then allowed to stand overnight at room temperature (20°), resulting in a brown slurry. This reaction mixture was evaporated to dryness under vacuo and the residue was repeatedly extracted with ethyl acetate (30 mL x 6). The collected extracts were evaporated to enable SiO_2 chromatography. At this point, a spectrophotometric determination was possible, by dissolving an aliquot in methanol and using the strong hyperconjugated isothiazine band at 218 nm. The SiO_2 preparative TLC was developed twice in CH_2Cl_2 (R_f 0.30). Elution of **2** from the scraped silica band with ethyl acetate (UV observation with a Desaga lamp at 254 nm) gave 52 mg (0.3 mmol, 30%). An analytical grade product (19 mg) was obtained by a second TLC purification on analytical plates, followed by crystallization in ethyl acetate-pentane, mp. 164-167°, lit.[1,5] mp. 164-167°, UV (MeOH, nm, ε): 218 (5x10^4), 245 (1.4x10^4), 264 (1.2 x10^4); MS *m/z* (%):174 M$^+$ (100), 147 M-HCN$^+$ (8), 146 (9), 142 (13); high resolution MS: Calc.for $C_9H_6N_2S$ 174.02517. Found 174.0257; ^{1}H NMR ($CDCl_3$): δ 7.27, t, 1H, $J_{6,7} = J_{5,6}$ = 8 Hz (H6); 7.37, t, 1H, $J_{4,5} = J_{5,6}$ = 8 HZ (H5); 7.45, d, 1H,

$J_{6,7}$ = 8 Hz (H7); 7.91, d, 1H, $J_{4,5}$ = 8 Hz (H4); 8.72, s, 1H (H3); 8.98, s, 1H (NH).

Acknowledgements.- Thanks are due to Drs B. C. Das, C. Girard and J. P. Dupuis for the mass spectrometric determinations carried out at Gif-sur-Yvette.

REFERENCES

1. M. Devys, M. Barbier, I. Loiselet, T. Rouxel, A. Sarniguet, A. Kollmann and J. F. Bousquet, *Tetrahedron Lett.*, **29**, 6447 (1988).

2. a) T. Rouxel, A. Sarniguet, A. Kollmann and J. F. Bousquet, *Physiol. Mol. Plant Pathol.*, **34**, 507 (1989); b)A. Kollmann, T. Rouxel and J. F. Bousquet, *J. Chromatogr.*, **473**, 293 (1989).

3. a) M. Takasugi, K. Monde, N. Katsui and A. Shirata, *Bull. Chem. Soc. Jpn*, **61**, 285 (1988); b) M. Takasugi, N. Katsui and A. Shirata, *Chem. Comm.*, 1077 (**1986**); c) M. Takasugi, K. Monde, N. Katsui and A. Shirata, *Chemistry Lett.*, 1631 (**1987**).

4. C. Tempête, M. Devys and M. Barbier, *Z. Naturforsch.*, **46c**, 706 (1991).

5. M. Devys and M. Barbier, *Synthesis*, 214 (**1990**).

6. a) M. Devys and M. Barbier, *J. Chem. Soc. Perkin Trans 1*, 2856 (1990); b) M. Devys and M. Barbier, *Z. Naturforsch.*, **47c**, 318 (1992).

7. M. Devys, M. Barbier, A. Kollmann, T. Rouxel and J. F. Bousquet, *Phytochem.*, **29**, 1087 (1990).

8. F. A. Davis, W. A. R. Slegeir, S. Evans, A. Schwartz, D. L. Goff and R. Palmer, *J. Org. Chem.*, **38**, 2809 (1973).

9. M. D. Bentley, I. B. Douglas, J. A. Lacadie, D. C. Weaver, F. A. Davis and S. J. Eitelman, *Chem. Comm.*, 1625 (**1971**).

****