

p-ANISYL GROUP: A VERSATILE PROTECTING GROUP FOR PRIMARY ALCOHOLS

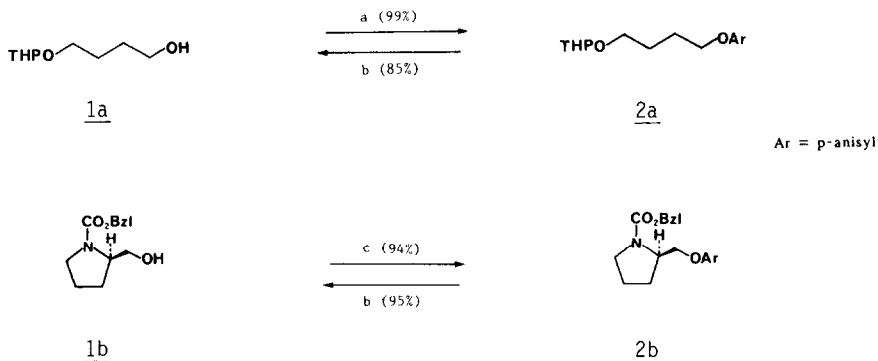
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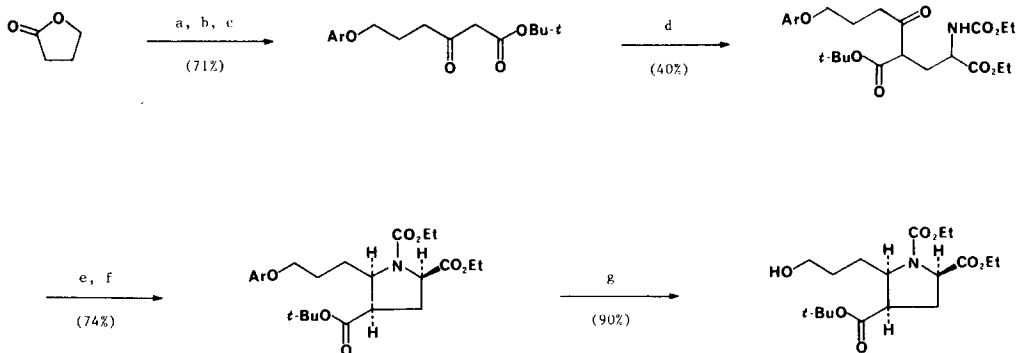
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Abstract: A primary alcohol can be protected as a highly stable p-anisyl ether, which undergoes mild oxidative deprotection by ceric ammonium nitrate.

Although numerous protecting groups for alcohols have been devised to date, none appears to be stable under strongly acidic, strongly basic, oxidative, and reductive conditions, and yet can be deprotected under mild conditions.<sup>1</sup> During the course of synthetic studies on naphthyridinomycin,<sup>2</sup> we needed a protecting group for a primary alcohol which should survive through a series of acidic, basic, and reductive reactions. We report herein that a primary alcohol<sup>3</sup> 1 can be readily converted to its sturdy p-anisyl ether 2 by means of Mitsunobu reaction.<sup>4,5</sup> The p-anisyl ether can withstand the following tested conditions: 3N HCl, 100°, 30 min; 3N NaOH, 100°, 30 min; H<sub>2</sub> (1200 psi), Raney Ni (W-2), EtOH, 100°, 2 hr; LiAlH<sub>4</sub>, THF, rt, 1 hr; Jones oxidation, rt; PCC, CH<sub>2</sub>Cl<sub>2</sub>, rt, 2 hr; O<sub>3</sub>, MeOH, -78°. Facile deprotection of the p-anisyl ether occurs by treatment with ceric ammonium nitrate (CAN) in aqueous acetonitrile at 0°. <sup>6,7</sup> The following examples clearly demonstrate the usefulness of our method:<sup>8</sup>



(a) p-methoxyphenol, Ph<sub>3</sub>P, diethyl azodicarboxylate, CH<sub>2</sub>Cl<sub>2</sub>, rt, 30 min; (b) CAN, CH<sub>3</sub>CN-H<sub>2</sub>O (4:1), 0°, 10 min; (c) p-methoxyphenol, Ph<sub>3</sub>P, diethyl azodicarboxylate, THF, 80°, 15 min.



(a) *p*-methoxyphenol, KOH, 160°; (b) SOCl<sub>2</sub>, benzene, reflux; (c) Meldrum's acid, Py, CH<sub>2</sub>Cl<sub>2</sub>, rt, then *t*-BuOH, toluene, reflux; (d) ethyl 2-carboethoxyaminoacrylate, Triton B, EtOH, rt; (e) CSA, quinoline, toluene, reflux; (f) H<sub>2</sub> (1200 psi), Rh/Al<sub>2</sub>O<sub>3</sub>, EtOH, 100°; (g) CAN, CH<sub>3</sub>CN-H<sub>2</sub>O (4:1), 0°.

**Acknowledgment:** This work was supported by Grant CA-28119, awarded by the National Institutes of Health, and by the Robert A. Welch Foundation.

#### References and Notes

- Green, T. W. "Protective Groups in Organic Synthesis," Wiley-Interscience: New York, 1981; pp 10-86.
- Sygyusch, J.; Brisse, F.; Hanessian, S.; Kluepfel, D. *Tetrahedron Lett.*, 1974, 4021, correct structural drawing is shown in errata, *Tetrahedron Lett.*, 1975, No. 3.
- For protection of secondary alcohols, Walden inversion should be taken into account.
- For a review of Mitsunobu reaction, see: Mitsunobu, O. *Synthesis*, 1981, 1.
- Alternatively, *p*-anisyl ether can be prepared from the corresponding mesylate and potassium *p*-methoxyphenoxide in DMF.
- Jacob, P., III; Callery, P. S.; Shulgin, A. T.; Castagnoli, N., Jr. *J. Org. Chem.*, 1976, 41, 3627.
- Similar protecting groups have been used for  $\beta$ -lactam synthesis: (a) Fukuyama, T.; Frank, R. K.; Jewell, C. F., Jr. *J. Am. Chem. Soc.*, 1980, 102, 2122. (b) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.*, 1982, 47, 2765.
- A representative procedure is as follows: A mixture of the alcohol **1b** (124 mg, 0.53 mmol), *p*-methoxyphenol (197 mg, 1.59 mmol), Ph<sub>3</sub>P (180 mg, 0.69 mmol), diethyl azodicarboxylate (114  $\mu$ l, 0.69 mmol), and dry THF (2 ml) in a culture tube was heated at 80° for 15 min. Evaporation and separation on a silica gel column (MPLC) afforded the ether **2b** (169 mg, 94%). To an ice-cold solution of the *p*-anisyl ether **2b** (162 mg, 0.475 mmol) in CH<sub>3</sub>CN-H<sub>2</sub>O (4:1, 6 ml) was added CAN (625 mg, 1.14 mmol) in one portion. After 10 min, the mixture was partitioned between EtOAc and brine. The organic layer was washed with a satd. NaHCO<sub>3</sub> solution, dried, evaporated, and chromatographed to give the alcohol **1b** (106 mg, 95%).

(Received in USA 25 September 1985)