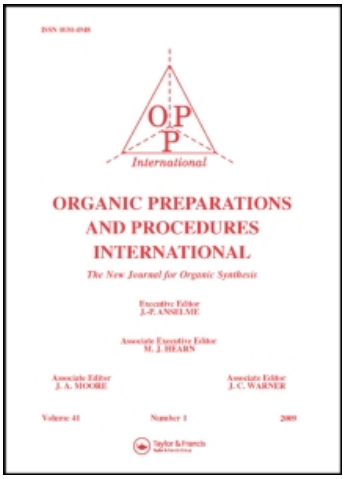


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

AN ALTERNATIVE METHOD FOR TOLNAFTATE

N. R. Ayyangar[a]; R. D. Wakharkar[a]; V. H. Deshpande[a]; B. Rai[a]
[a] National Chemical Laboratory, Pune, INDIA

To cite this Article Ayyangar, N. R. , Wakharkar, R. D. , Deshpande, V. H. and Rai, B.(1990) 'AN ALTERNATIVE METHOD FOR TOLNAFTATE', Organic Preparations and Procedures International, 22: 1, 128 — 130
To link to this Article: DOI: 10.1080/00304949009356685
URL: http://dx.doi.org/10.1080/00304949009356685

REFERENCES

1. A. Kalir, H. Edery, Z. Pelah, D. Balderman and G. Porath, J. Med. Chem., 12, 473 (1969).

2. D. C. K. Lin, A. F. Fentiman, Jr., R. L. Foltz, R. D. Forney, Jr. and I. Sunshine, Biomed. Mass Spectrom., 2, 206 (1975).

3. a) J. K. Baker, J. G. Wohlford, B. J. Bradbury and P. W. Wirth, J. Med. Chem., 24, 666 (1981); b) L. S. Cohen, L. Gosenfeld. J. Wilkins, R. C. Kammerer and K. Tachiki, N. Engl. J. Med., 306, 1427 (1982).

4. S. M. Owens, M. Zorbas, D. L. Lattin, M. Gunnel and M. Polk, J. Pharmacol. Exp. Ther., 246, 472 (1988).

5. C. H. Tilford, L. A. Doerle, M. G. van Campen, Jr. and R. S. Shelton, J. Am. Chem. Soc., 71, 1705 (1949).

6. a) U. S. Patent 2,921,076 (January 12, 1960); Chem. Abstr., 54, 12159a (1960); b) British Patent 838,748 (June 22, 1960); Chem. Abstr., 55, 2692a (1961).

7. A reaction temperature of 45-50° avoided the problems of elimination (reflux conditions), incomplete reaction and prolonged reaction time (room temperature conditions).

****

AN ALTERNATIVE METHOD FOR TOLNAFTATE †

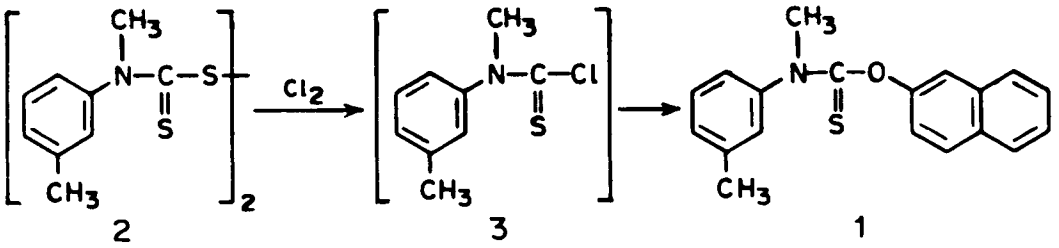
Submitted by (05/17/89) N. R. Ayyangar*, R. D. Wakharkar
V. H. Deshpande and B. Rai

National Chemical Laboratory
Pune 411008, INDIA

The utility of tolnaftate [2-naphthyl-N-methyl-N-(m-tolyl) thionocarbamate, 1], a two-step condensation product of N-methyl-m-toluidine, thiophosgene and β-naphthol,[1,2] as an effective antifungal drug has been known for more than a decade. We now communicate an alternative method which avoids the use of thiophosgene for its preparation and employs carbon disulphide and chloride (absorbed in CCl_4).[3]

Methylation of N-acetyl-m-toluidine in presence of PTC followed by hydrolysis provided N-methyl-m-toluidine, in nearly quantitative yield.[4] The dimethyl di-(m-tolyl)thiuram disulphide (2) was prepared [5] from N-methyl-m-toluidine by treatment with excess of carbon disulphide in the presence of iodine and pyridine. It was then converted into N-methyl-N-(m-tolyl)thiocarbamoyl chloride (3) in excellent yields by treatment with requisite amount of chlorine absorbed in carbon tetrachloride at 5-10°. The thiocarbamoyl chloride 3 was condensed, without further purification, with β -naphthol in refluxing benzene in the presence of powdered potassium

hydroxide and a phase-transfer catalyst (tetrabutylammonium bromide) to give tolnaftate 1 in 80% yield. In the absence of potassium hydroxide and tetrabutylammonium bromide the yield of 1 was only 65%.



EXPERIMENTAL SECTION

IR spectra were recorded on a Perkin-Elmer spectrometer. NMR spectra were obtained on Jeol-60 spectrometer using Me_4Si as an internal standard. Mass spectral analyses were determined using Finnigan MAT automated GC/MS 1020 electron impact, 70 ev. All mps were uncorrected.

Dimethyl di-(m-tolyl)thiuram disulphide (2).- The title compound was prepared by a known method[5] with a modified work-up procedure. After completion of the reaction, the mixture was cooled to room temperature, diluted with water and the product was collected by filtration in 70% yield, mp 170°, lit.[5] 170.5°.

2-Naphthyl-N-methyl-N-(m-tolyl)thionocarbamate (Tolnaftate 1).- To a stirred solution of the thiuram disulphide 2 (19.6 g, 0.05 mole) in 50 ml of carbon tetrachloride was added a solution of chlorine (3.5 g, 0.1 mole) in carbon tetrachloride (30 ml) at 5-10°. Stirring was continued for 5 hrs. The reaction was monitored by TLC (silica gel, 9:1 pet ether-ethyl acetate). The solvent was removed under reduced pressure and the product was extracted into petroleum ether. After removal of solvent, the residue (19.85 g) was dissolved in 20 ml benzene and added to a mixture containing powdered potassium hydroxide (11 g, 0.2 mole), β-naphthol (14.4 g, 0.1 mole) and tetrabutylammonium bromide (200 mg) in 50 ml benzene at room temperature. After completion of the addition, the reaction mixture was refluxed for 5 hrs, cooled to room temperature, washed with water and dried over sodium sulphate. The solvent was removed completely under vacuum and the crude product (30 g) was purified by passing through a column of silica gel using 9:1 petroleum ether-ethyl acetate as solvent system to afford 24.6 g (80%) of colorless crystalline tolnaftate (1), mp. 110°, lit.[6] 110.5-111.5°, 109-112°, identical with a commercial sample. IR (nujol): 1620, 1600, 1580, 1460 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.27 (s, 3H, m-CH_3), 3.58 (s, 3H, N-CH_3), 6.9-7.85 (m, 11H, aromatic). MS: M^+ 307.

Anal. Calcd for $C_{19}H_{17}NOS$: C, 74.23; H, 5.58; N, 4.56; S, 10.43

Found: C, 74.05; H, 5.63; N, 4.75; S, 10.70

Acknowledgement.- One of the authors (B. Rai) is thankful to the CSIR, New Delhi for financial support.

REFERENCES

† NCL Communication No. 4686

1. B. Rainer and S. Eva, Ger (East) Patent, 128,369 (1977); C. A. 89, P24039 h (1978).

2. Japan Soda Co. Ltd., Fr. Patent, 1,337,797 (1963), C. A. 60: P2871 b (1964); Japan Soda Co. Ltd., Bdg. 627,322 (1963), C. A. 60: P7969 (1964); T. Noguchi, Y. Hashimoto, K. Miyazaki, A. Kaji, (Nippon Soda Co. Ltd., Oise, Japan). Yakugaku Zasshi, 88 (3), 335 (1968), C. A. 69: 76987 x (1968).

3. Transporation, storage and handling in large quantities of these chemicals, although hazardous, are well studied and they are commonly used industrially.

4. N. R. Ayyangar, A. R. Chaudhary, U. R. Kalkote and A. A. Natu, Synth. Commun., 18, 2011 (1988).

5. H. S. Fry and B. S. Farquhar, Rec. Trav. Chim. Pays-Bas, 57 1223 (1938).

6. The Merck Index, 10th Ed., 9347 (1983); British Pharmacopoeia 1, 578 (1988).

****