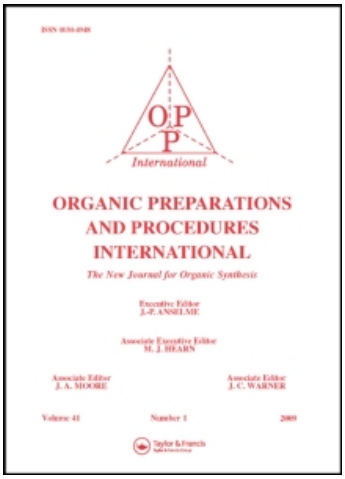


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SYNTHESIS OF 1,3-DIMETHYLAZULENE

Nicholas M. Irvine[a]; Marek Majewski[a]
[a] Department of Chemistry, University of Saskatchewan, Saskatoon, Saskatchewan, CANADA

To cite this Article Irvine, Nicholas M. and Majewski, Marek(1995) 'SYNTHESIS OF 1,3-DIMETHYLAZULENE', Organic Preparations and Procedures International, 27: 5, 592 — 595
To link to this Article: DOI: 10.1080/00304949509458513
URL: http://dx.doi.org/10.1080/00304949509458513

REFERENCES

1. *Chemical & Engineering News*, November 21, 1994, p. 12.

2. H. Mrozik, R. J. Bochis, P. Eskola, A. Matzuk, F. S. Waksmunski, L. E. Olen, G. Schwartzkopf, Jr., A. Grodski, B. O. Linn, A. Lusi, M. T. Wu, C. H. Shunk, L. H. Peterson, J. D. Milkowski, D. R. Hoff, P. Kulsa, D. A. Ostlind, W. C. Campbell, R. F. Riek and R. E. Harmon, *J. Med. Chem.*, **20**, 1225 (1977).

3. a) E. D. Bergmann, D. Ginsburg and D. Lavie, *J. Am. Chem. Soc.*, **72**, 5012 (1950); b) E. L. Compere, Jr., *J. Org. Chem.*, **33**, 2565 (1968).

4. a) P. J. Atkins and V. Gold, *Chem. Commun.*, 140 (1983); b) P. J. Atkins, V. Gold and W. N. Wassef, *ibid.*, 283 (1983).

5. J. M. Wyvratt, G. G. Hazen and L. M. Weinstock, *J. Org. Chem.*, **52**, 944 (1987).

6. H. Matsumoto, Y. Hoshino, J. Nakabayashi, T. Nakano and Y. Nagai, *Chemistry Lett.*, 1475 (1980).

7. a) J. M. Renga and P. - C. Wang, *Tetrahedron Lett.*, **26**, 1175 (1985); b) M. A. de Jesus, J. A. Prieto, L. del Valle and G. L. Larson, *Syn. Comm.*, **17**, 1047 (1987).

8. For a proposed mechanism, see ref. 7a.

9. The solvent switch to THF is necessary as the reaction does not proceed in toluene.

10. J. Weichet and J. Hodra, *Collect. Czech. Chem. Commun.*, **22**, 511 (1957).

****

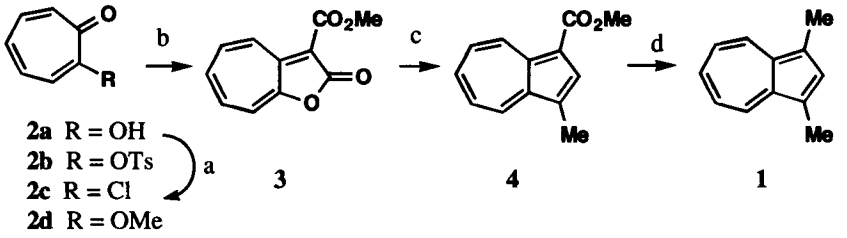
SYNTHESIS OF 1,3-DIMETHYLAZULENE

Submitted by (03/28/95) Nicholas M. Irvine and Marek Majewski*

Department of Chemistry, University of Saskatchewan
Saskatoon, Saskatchewan, CANADA, S7N 0W0

Azulene and substituted azulenes (e.g., **1**) continue to attract attention of researchers (both chemists and non-chemists alike) due to their unusual spectral, chemical and physiological properties.[1,2] Although a number of methods for preparing alkylazulenes exist, many of the older methods incorporate at least one very inefficient step.[1,3] Amongst the newer methods, the Ziegler-Hafner synthesis from cyclopentadiene[4] (annulation of a seven-membered ring) and the enamine method,[5] based on 3-substi-

tuted-2H-cyclohepta[b]furan-2-ones (**3**) being the critical intermediates (annulation of a five-membered ring), proved very useful. Several other methods of synthesis of substituted azulenes e.g., by aminoalkylation or acylation of azulene,[6] by addition of tropylium cation to allenylsilanes,[7] by iron carbonyl-aided coupling of α,α-dibromoketones and enamines,[8] were also reported. Below, we describe the application of the enamine method to synthesis of 1,3-dimethylazulene (**1**).



a) CH_2N_2; b) NaH, $CH_2(COOMe)_2$; c) morpholine, propanal; d) $LiAlH_4/AlCl_3$

The key intermediate for synthesis of substituted azulenes by the enamine method, compound **3**, can be prepared from either 2-tosyloxy-, 2-chloro-, or 2-methoxytropone (**2b**, **2c** or **2d**).[5] All three precursors must be synthesized from tropolone (**2a**).[9] In our hands, the synthesis of **2d** from tropolone and CH_2N_2, following a known procedure,[9] was cleaner and gave higher yield (97%) than the synthesis of **2c** by chlorination of tropolone. The subsequent condensation of 2-methoxytropone **2d** with sodium enolate of dimethylmalonate gave compound **3** in a modest yield (53%). Conversion of **3** to the azulene carboxylate **4**, according to Yasunami's procedure (condensation with morpholine and propanal[5e]), proceeded smoothly and the ester **4** was produced in 96% yield. The ester group was then reduced to the methyl by $LiAlH_4$-$AlCl_3$, similar conditions were used earlier by a Japanese team in reduction of 3-formylguaiazulene to the corresponding alkane.[10]

In summary, the enamine method provides a good entry into dialkylazulenes. The four step synthesis of 1,3-dimethylazulene, described above, proceeded in 43% overall yield (from tropolone) which compares favorably with other strategies. Other alkyl and dialkylazulenes can be synthesized by this method using different aldehydes or ketones instead of propanal.

EXPERIMENTAL SECTION

Melting and boiling points are uncorrected. The NMR spectra were obtained on a Bruker AM-300 spectrometer at 300 MHz in $CDCl_3$ using TMS as internal standard. Diazomethane was prepared from Diazald^R supplied by Aldrich (CAUTION: explosion hazard. Refer to the Aldrich information sheet attached to Diazald for a safe procedure or send for Aldrich Bulletin No. AL-180). Tropolone was purchased from Aldrich and used without purification.

2-Methoxytropone (2d).[9a] - A solution of tropolone (**2a**, 1.10 g, 9.0 mmol) in Et_2O (30 mL) and MeOH (3 mL) was treated dropwise over 10 min., with a solution of CH_2N_2 in Et_2O. The reaction was monitored by methanolic $FeCl_3$ and was stopped when a drop of the reaction mixture gave no

coloration of $FeCl_3$. The solvent was removed *in vacuo* and the residue was distilled under reduced pressure (Kugelrohr) to afford 1.19 g (97%) of a pale yellow liquid, bp. 175°/0.5 mm Hg. ^1H NMR: δ 3.89 (s, 3H), 6.68-7.19 (m, 5H).

3-Methoxycarbonyl-2H-cyclohepta[b]furan-2-one (3).- This compound was prepared according to a literature procedure.[5b,c] Dimethyl malonate (0.50 mL, 4.4 mmol) was added slowly to a suspension of NaH (0.10 g, 4.3 mmol) in anhydrous THF (20 mL) under argon. After 15 minutes, a solution of **2d** (0.30 g, 2.2 mmol) in THF was added and the reaction mixture was gently refluxed for 2 hrs. The solution was then cooled to rt., diluted with Et_2O (50 mL) and quenched with 10% HCl (10 mL). The aqueous layer was extracted with Et_2O and the combined organic layers were washed with water and brine and dried ($MgSO_4$). After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography (alumina, 2% acetone in CH_2Cl_2) followed by recrystallization from EtOH to afford compound **3** as a yellow solid (0.24 g, 53%), mp. 166-169°, lit.[5f] mp. 173-174°, ^1H NMR: δ 3.94 (s, 3H), 7.30-7.65 (m, 4H), 8.86 (d, 1H).

Methyl 3-methylazulene-1-carboxylate (4).[5e] - Morpholine (0.64 mL, 7.35 mmol) was added to a mixture of compound **3** (0.50 g, 2.45 mmol) and propanal (0.53 mL; 7.25 mmol) in dry EtOH (8 mL). The mixture was refluxed for 3 hrs, cooled to rt., and the solvent was removed under vacuum. The residue was dissolved in benzene, the resulting solution was washed with H_2O, dried (Na_2SO_4), and the solvent was removed. The crude product was purified by chromatography (SiO_2, 10% AcOEt in hexane) followed by recrystallization from hexane to yield **4** as a dark violet solid (0.51 g, 96%), mp. 65-68°, lit.[5e] mp. 69-70°; ^1H-NMR: δ 2.61 (s, 3H), 3.93 (s, 3H), 7.41 (m, 2H), 7.74 (pseudo t, J=10 Hz, 1H), 8.19 (s, 1H), 8.33 (d, J=10 Hz, 1H), 9.54 (d, J=10 Hz, 1H).

1,3-Dimethylazulene (1).- Anhydrous $AlCl_3$ (0.12 g, 0.88 mmol) was added over 10 min *via* a side arm attachment to a suspension of $LiAlH_4$ (0.033 g, 0.88 mmol) in anhydrous Et_2O (0.5 mL) at 0° under Ar. A solution of **4** (0.095 g, 0.44 mmol) in anhydrous Et_2O (2 mL) was then added over 15 min. After an additional 10 min at 0°, Et_2O (10 mL) was added and the mixture was quenched slowly with aqueous 2N NaOH (1 mL). The organic layer was decanted and the insoluble material was washed thoroughly with Et_2O. The organic layers were combined, washed with brine and dried over Na_2SO_4. Purification of the residue by column chromatography (alumina, hexane) provided 1,3-dimethylazulene (0.066 g, 87%), mp. 53-54°, lit.[3a] mp. 54°; ^1H NMR: δ 2.63 (s, 6H), 6,92 (t, J = 9.7 Hz), 7.43 (t, J = 9.8 Hz, 1H), 7.58 (s, 1H), 8.09 (d, J = 9.3 Hz, 2H).

REFERENCES

1. D. Lloyd, *Non-benzenoid Conjugated Carbocyclic Compounds*. Elsevier, Amsterdam, **1984**, pp 352-377.

2. K. P. Zeller in *Methoden der Organischen Chemie*, H. Kropf, Ed., Thieme Verlag, Stuttgart, **1985**; Vol. V-2c, pp. 127-418.

3. a) P. A. Plattner, A. Furst and K. Jirasek, *Helv.*, **30**, 1320 (1947); b) T. M. Jacob, P. A. Vatak-

encherry and Sukh Dev, *Tetrahedron*, **20**, 2815 (1964).

4. K. Hafner and K.-P. Meinhardt, *Org. Synth., Coll. Vol. 7*, 15 (**1990**).

5. a) T. Nozoe, K. Takase and N. Shimazaki, *Bull. Chem. Soc. Jpn*, **37**, 1644 (1964); b) T. Nozoe, K. Takase, T. Nakazawa and S. Fukuda, *Tetrahedron*, **27**, 3357 (1971); c) K. Takase, M. Yasunami, T. Tomiyama, I. Tomiyama, T. Yanagisawa, M. Okutsu, and T. Meguro, JP 60202816 A2; *CA*, **104**: 109459y (1986); d) T. Nozoe, H. Wakabayashi, S. Ishikawa, C.-P. Wu and P.-W. Yang, *Heterocycles*, **31**, 17 (1990); e) M. Yasunami, S. Miyoshi, N. Kanegae and K. Takase, *Bull. Chem. Soc. Jpn*, **66**, 892 (1993); f) A. Mori, Y. Nukii, H. Takashita and T. Nozoe, *Heterocycles*, **35**, 863 (1993).

6. a) A. G. Anderson and R. D. Breazeale, *J. Org. Chem.*, **34**, 2375 (1969); b) G. R. Sacco, *J. Chem. Eng. Data*, **17**, 386 (1972).

7. D. A. Becker and R. L. Danheiser, *J. Am. Chem. Soc.*, **111**, 389 (1989).

8. Y. Hayakawa, K. Yokoyama and R. Noyori, *ibid.*, **100**, 1799 (1978).

9. a) W.v. E. Doering and L. H. Knox, *ibid.*, **73**, 828 (1951); b) W. v. E. Doering and L. H. Knox, *ibid.*, **74**, 5683 (1952).

10. M. Yamaguchi, *Nippon Kagaku Kaishi*, **7**, (1982); *CA*, **97**: 181908y (1982).

****

SYNTHESIS OF ACETOXYLATED AND HYDROXYLATED NITROBENZO[a]PYRENE AND NITROBENZO[e]PYRENE

Submitted by (01/05/95) M.-J. Lee, J.-S. Lai, E. Cheng and P. P. Fu*†

Institute of Chemistry, Providence University, Sha-lu Taichung, Taiwan, Rep. of CHINA

† *National Center for Toxicological Research, Jefferson, AR 72079*

Hydroxylated and acetoxylated polycyclic aromatic hydrocarbons (PAHs) have been detected in the environment[1,2] and some of these compounds exhibit higher mutagenic activity than their respective parent nitro-PAHs.[3-5] Hydroxylated nitro-PAHs are also principal metabolites of nitro-PAHs.[3,4] Thus, these compounds may pose possible adverse human health effects. Synthetic standards are required to study their genotoxic and other biological activity. This paper reports the synthesis of