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Microwave-assisted Michael reactions of 3-(2′-nitrovinyl)indole with indoles on TLC-grade silica gel. A new, facile synthesis of 2,2-bis(3′-indolyl)nitroethanes

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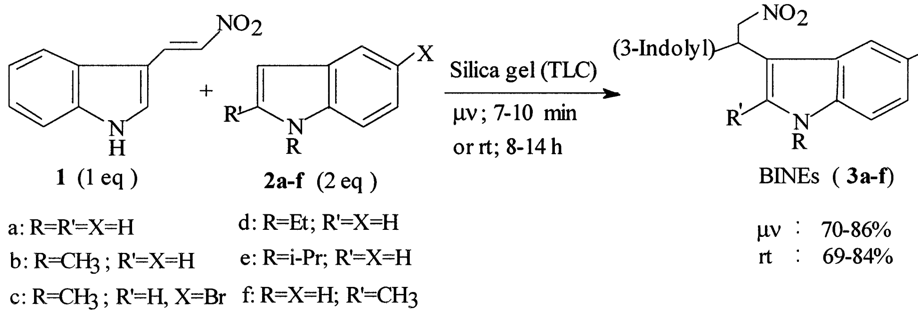
Abstract—3-(2′-Nitrovinyl)indole reacted with indole and 1- and 2-alkylindoles on TLC-grade silica gel under microwave irradiation to furnish in 7–10 min bis(indolyl)nitroethanes in high yields (70–86%). The same products were also obtained in 69–84% yields without microwave irradiation, but the reactions required 8–14 h for completion. Skatole was inert under both sets of conditions. © 2001 Elsevier Science Ltd. All rights reserved.

Bisindolylalkanes and their derivatives constitute an important group of bioactive metabolites of terrestrial and marine origin.[1a–f] A few of these are 2,2-bis(3′-indolyl)ethylamines (BIEAs) isolated recently from tunicates and sponges.[1c,d] Although a number of BIEAs had earlier been prepared by the reaction of indolic Grignard reagents or indoles with *N*-acyl or *N*,*N*-dialkylaminoalkanals or their diethyl acetals[2,3] and by the reduction of 2,2-bis(3′-indolyl)acetamides by lithium aluminium hydride,[3] the first synthesis of a naturally occurring BIEA, viz. 2,2-bis(6′-bromo-3′-indolyl)-ethylamine has been accomplished only recently. This general method involves the reaction of indoles with nitrones or 3-indolylhydroxylamines to furnish both symmetrical and unsymmetrical BIEAs.[4,5] The two main synthetic routes[3–5] to BIEAs involve in most cases long reaction periods (up to 72 h) and furnish the BIEAs in wide-ranging yields (2–100%).

Prompted by these recent reports of the isolation of BIEAs as natural products, their potential and the new syntheses thereof, we present herein a new, extremely facile and efficient synthesis of 2,2-bis(3′-indolyl)nitroethanes (BINEs). In view of the expected easy reducibility of nitroalkanes to alkylamines,[6] the present method offers a formal entry to BIEAs. Thus, the condensation of 3-(2′-nitrovinyl)indole (**1**), prepared by the Henry reaction of 3-formylindole[7] with indole and 1- and 2-alkylindoles (**2a**–**f**), both adsorbed on TLC-grade silica gel, furnished under microwave irradiation the BINEs **3a**–**f** in high yields (70–86%) (Scheme 1).[8] The reactions were remarkably fast, complete



Scheme 1.

Keywords: nitrovinylindole; microwave; solid surface; Michael reaction; bisindolylnitroethanes.

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Table 1. Results of μν-assisted reactions of **1** with indoles

BINE	Mp (°C)	μν		Rt	
		Time (min)	Yield (%)	Time (h)	Yield (%)
3a	64–66	10	86	14	82
3b	174	9	85	9	84
3c	[a]	9	73	10	72
3d	135–136	8.5	71	8	70
3e	142	9	75	9.5	72
3f	207–208	7	70	8	69

[a] Could not be crystallised.

within 10 min, and the products were isolated easily and identified from spectroscopic data.

The combined presence of a one-proton triplet at δ 5.38–5.51 and a two-proton doublet at δ 5.01–5.10 in their ^{1}H NMR spectra and the appearance of peaks at M-60 in the mass spectra of the products supported their 2,2-disubstituted nitroethane structures.

These reactions were also accomplished on TLC-grade silica gel alone, i.e. without microwave irradiation, at room temperature, when **3a**–**f** were obtained in comparable yields (69–84%). But the reactions took a considerably long time (8–14 h) for completion (Scheme 1, Table 1). For a comparative evaluation of the efficacy of the reactions with and without microwave irradiation, the progress of the reaction of **1** with **2a**, carried out without applying microwaves, was checked by TLC 10 min after mixing them on silica gel (TLC-grade). No product appeared to have been formed, which suggested that it is the microwave-effect[9] which was largely responsible for the observed higher efficacy of the microwave-assisted reactions. The presence of TLC-grade silica gel was found to be essential for success under both sets of conditions, since column-grade silica gel failed to bring about the reactions in both cases. Presumably, the failure of column-grade silica gel even under microwave heating is associated with its larger particle size (125–250 μ) than that of TLC-grade silica gel (5–40 μ).

Compounds **3a**–**f** were clearly the products of a Michael reaction of the nucleophilic indoles **2a**–**f** at C-1′ of the nitrovinylindole **1**. To our knowledge, this is the first report of a Michael reaction of the nitrovinylindole system using indoles as the nucleophiles, leading to an eco-friendly synthesis of the BINEs. This is the second report of a general synthesis of unsymmetrical diindolylalkanes (**3b**–**f**), the earlier one being the trimethylsilyl chloride-catalysed condensation of indoles with 3-indolylhydroxylamines.[4,5] The present method can also be employed for the synthesis of symmetrical diindolylalkanes, e.g. **3a** by using similarly substituted nitrovinylindoles and indoles. Since the nitro group can be converted into a variety of other functionalities, our methodology is likely to be of still wider application. We are currently engaged in such endeavours.

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8. *Reaction under microwave irradiation*: In a typical experiment, a solution of **1** (0.4 mmol) and 1-methylindole (**2b**) (0.8 mmol) in EtOAc (5 ml) was adsorbed on silica gel G (3 g) and the solvent was allowed to evaporate off at rt. The resulting dry mass was irradiated with microwaves (BPL-SANYO, 800 Watt, 50% power). When **1** was consumed (9 min), the reaction mixture was cooled to rt, the organic matter leached with EtOAc (3×20 ml), filtered through a bed of Celite and the residue obtained from the filtrate was purified by prep. TLC (silica gel, C_6H_6) to furnish **3b**, mp 174°C (petrol–$CHCl_3$) in 85% yield (0.11 g); IR (KBr): 3404, 1547, 1378, 746 cm^{-1}; EIMS: m/z 319 (M$^+$), 259; ^{1}H NMR ($CDCl_3$; 500 MHz): δ 3.70 (3H, s, NMe), 5.08 (2H, d, J 8 Hz, CH_2), 5.29 (1H, t, J 8 Hz, CH), 6.89 (1H, s), 7.04 (1H, d, J 2.5 Hz), 7.10 (2H, t, J 7.5

Hz), 7.20 and 7.24 (1H, t each, *J* 8 Hz), 7.30 and 7.35 (1H, d each, *J* 8 Hz), 7.60 (2H, d, *J* 8 Hz), 8.1 (1H, br s, NH); ^{13}C NMR (125 MHz): δ 33.1 (CH_3), 79.6 (CH_2), 34.1 (CH), 113.0, 114.8, 126.5, 126.9, 137.0, 137.7 (all Ar-C), 109.9, 111.8, 119.43, 119.45, 119.7, 120.2, 122.4, 122.6, 122.8, 127.4 (all Ar-CH). All other products were similarly identified by IR, MS, ^{1}H and ^{13}C NMR, DEPT 135, HMQC and HMBC spectra.

Reaction at rt: The reactants adsorbed on silica gel G as above were left at rt until **1** was consumed. The products were isolated as above and identified by comparison (mp, mmp, co-TLC) with samples obtained from the above microwave-assisted experiments.

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