Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 5099–5102
Tetrahedron Letters

Amberlyst 15 catalyzed synthesis of indole–pyrazole based tri(hetero)arylmethanes ☆

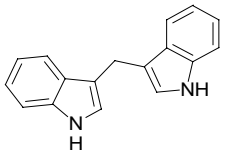
Farhanullah,[a] Ashoke Sharon,[b] Prakas R. Maulik[b] and Vishnu Ji Ram[a,*]

[a]*Divisions of Medicinal Chemistry, Central Drug Research Institute, Lucknow 226001, India*
[b]*Molecular and Structural Biology, Central Drug Research Institute, Lucknow 226001, India*

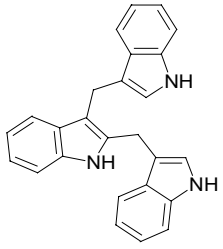
Received 11 March 2004; revised 22 April 2004; accepted 29 April 2004

Abstract—An expedient synthesis of 1,3-diaryl-4-(3,3′-diindolyl)methylpyrazoles **3a**–**m** has been developed using Amberlyst 15 catalyzed condensation of 1,3-diaryl-4-formyl pyrazoles **2** with indoles **1**. This reaction was further extended to the synthesis of 4,4′-bis(3,3′-diindolyl)methylphenoxy-alkanes **5a**–**b** by coupling of 4,4′–di(formylphenoxy)alkane **4** with indole **1**.

Indole, being an integral part of many natural products of therapeutic importance, possesses potentially reactive sites for a variety of chemical reactions to generate molecular diversity. This manuscript describes our efforts to synthesize indole based tri(hetero)arylmethanes by exploiting the reactivity of indole. Among various indole derivatives, diindol-3-yl-methane **I** and 2-(indol-3-yl-methyl)-3,3′-diindolylmethane **II** display diverse pharmacological activities and are useful in the treatment of fibromyalgia, chronic fatigue and irritable bowel syndrome.[1]



I



II

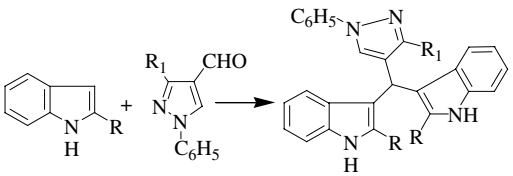
These compounds also inhibit the proliferation of both estrogen dependent and independent cultured breast tumor cells.[2,3] The therapeutic importance of diindolyl- and triindolylmethanes has aroused considerable interest in developing concise and economical indole–pyrazole and indole-oxyaryl based systems **3**, **5**. There are a few examples in the literature where indole-based tripods have been synthesized through condensation[4] of indole with triethyl orthoformate or by acylation[5] of indole with 2-alkoxy-1,3-dioxolanes. Protic acids[6a] as well as Lewis acids[6b] are reported to promote these reactions. An independent synthesis of diindol-3-yl-methanes **I** has been reported[7] earlier by anodic oxidation of an indole–cyclodextrin alcohol system and also by using lanthanide triflates,[8] indium chloride[9] and lithium perchlorate[10] as catalysts. Recently, bisindolyl methanes have been prepared using molecular iodine as a catalyst under mild reaction conditions.[11] We now report a very efficient, economical and convenient synthesis of 1,3-diaryl-4-(3,3′-diindolyl)methylpyrazoles **3a**–**m** in high yields via Amberlyst 15 catalyzed condensation of indole and 1,3-diaryl-4-formyl pyrazoles[12] **2**. This reaction was further explored for the synthesis of 4,4′-bis[(3,3′-diindolyl)methylphenoxy]alkanes **5a**–**b**, by the condensation of 4,4′-di(formylphenoxy)alkanes[13] **4** with indole in chloroform at ambient temperature in good yields. The methodology we report here is comparable in yield and far superior to the existing procedures, in having mild reaction conditions, an easy work-up and a reusable catalyst.

All the synthesized compounds (Table 1 and Scheme 1) were characterized[14] by spectroscopic and elemental analyses. The structure of one of the compounds, **3e**,

Keywords: Amberlyst 15; Coupling reaction; Tripodal-heterocycles.
☆ CDRI communication no: 6207.
* Corresponding author. Tel.: +91-522-2212411-4381; fax: +91-522-2223405; e-mail: vjiram@yahoo.com

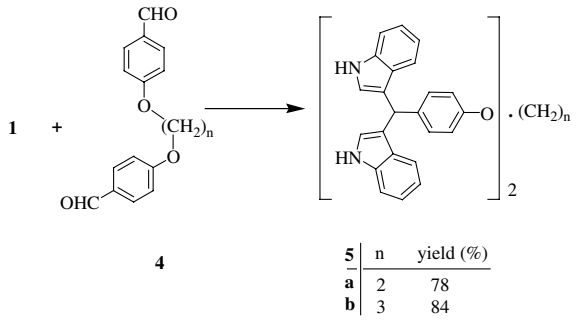
0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.04.172

Table 1



1 **2** **3**

3	R_1	R	Yield (%)
a	C_6H_5	H	85
b	4-$CH_3C_6H_4$	H	86
c	4-$H_3COC_6H_4$	H	96
d	4-FC_6H_4	H	83
e	4-ClC_6H_4	H	80
f	4-BrC_6H_4	H	90
g	2-Thienyl	H	78
h	C_6H_5	C_6H_5	81
i	4-$CH_3C_6H_4$	C_6H_5	86
j	4-$H_3COC_6H_4$	C_6H_5	85
k	4-FC_6H_4	C_6H_5	84
l	4-ClC_6H_4	C_6H_5	77
m	4-BrC_6H_4	C_6H_5	88



4

5	n	yield (%)
a	2	78
b	3	84

Scheme 1.

was further confirmed by single crystal X-ray diffraction.[15]

The ORTEP view, Figure 1 shows the crystal structure of **3e** and its conformation with atomic numbering scheme. The central C10-atom is tetrahedrally substituted with two planar indoles and one disubstituted pyrazole. The phenyl and chlorophenyl substituents on N20 and C22 atoms are twisted at 34.5 (3)° and 42.3 (3)° respectively from the mean plane of the pyrazole ring. The crystal packing reveals the presence of weak intermolecular N–H...N, C–H...π and N–H...π interactions. The molecule contains two potential hydrogen bond donors (–NH groups N1–H1 and N11–H11) of which one is involved in intermolecular hydrogen bonding with N21 (N1–H1...N21: 3.201 Å). The other donor, N11–H11, is involved in intermolecular N–H...π interaction with one of the fused phenyl rings of an indole (minimum distance H11...C7: 2.691 Å). The molecule crystallizes with two $CHCl_3$ solvent molecules in one asymmetric unit. One of these solvent molecules is involved in intermolecular C–H...π interaction with the

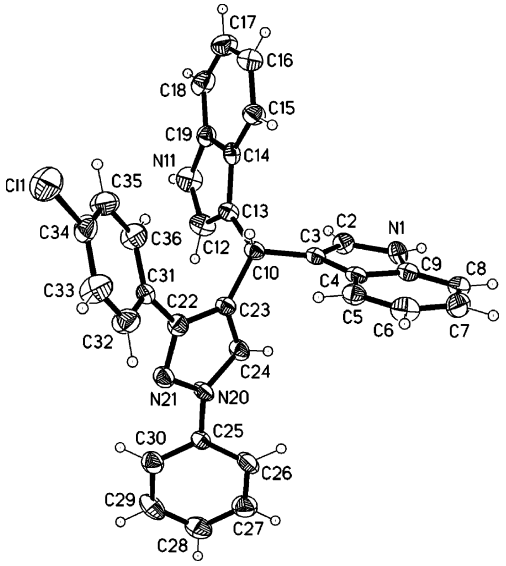


Figure 1. ORTEP diagram of the molecular structure of **3e**.

pyrazole linked phenyl ring at N20 (minimum distance H38...C30: 3.263 Å).

Thus, these weak interactions play a fundamental role in the three-dimensional organization of these molecules in the solid state.[16]

Acknowledgements

Farhanullah and Ashoke Sharon thank CSIR, New Delhi for Senior Research Fellowships. The authors thank SAIF, CDRI, Lucknow for providing spectroscopic data.

References and notes

1. (a) Kathleen, A.; Merrill, A. G. PCT. Int. Appl. WO 99, *Chem. Abstr*. **1999**, *130*, 276765p; (b) Bradfield, C. A.; Bjeldanes, L. F. *J. Toxicol. Environ. Health* **1987**, *21*, 311–323; (c) Dashwood, R. H.; Uyetake, L.; Fong, A. T.; Hendricks, J. D.; Bailey, G. S. *Food Chem. Toxicol.* **1987**, *27*, 385–392.
2. (a) Ge, Xiaokang; Fares, F. A.; Yannai, S. *Chem. Abstr.* **2000**, *133*, 73462b; (b) Chang, Yu-Chen; Riby, J.; Chang, Grace H. F.; Peng, G. F.; Bjeldanes, L. F. *Biochem. Pharmacol.* **1999**, *58*, 825–834.
3. (a) Shilling, A. D.; Carlson, D. B.; Katchamart, S.; Williams, D. *Appl. Pharmacol.* **2001**, *170*, 191–200; (b) Ge, X.; Yannai, S.; Rennert, G.; Gruener, N.; Fares, F. A. *Biochem. Biophys. Res. Commun.* **1996**, *228*, 153–158; (c) Ge, X.; Fares, F. A.; Yannai, S. *Anticancer Res.* **1999**, *19*, 3199–3203.
4. Akgün, E.; Pindur, U.; Müller, J. *J. Heterocycl. Chem.* **1983**, *20*, 1303–1305.
5. Akgün, E.; Tunali, M.; Pindur, U. *Arch. Pharm.* **1987**, *320*, 397–401.
6. (a) Korolev, A. M.; Yudina, L. N.; Lazhko, E. I.; Reznikova, M. I.; Preobrazhenskaya, M. N. *Chem.*

Heterocycl. Compd. (NY) **1999**, *35*, 561–569; (b) Roomi, M.; MacDonald, S. I. *Can. J. Chem.* **1970**, *48*, 139–143; (c) Woland, W.; Venkiteswaren, M.; Richards, C. *J. Org. Chem.* **1961**, *26*, 4241–4248.
7. Suda, K.; Takanami, T. *Chem. Lett.* **1994**, 1915–1916.
8. Chen, D.; Yu, L.; Wang, P. G. *Tetrahedron Lett.* **1996**, *37*, 4467–4470.
9. Babu, G.; Sridhar, N.; Perumal, P. T. *Synth. Commun.* **2000**, *30*, 1609–1614.
10. (a) Yadav, J. S.; Reddy, B. V. S.; Murthy, Ch. V. S. R.; Kumar, G. M.; Madan, Ch. *Synthesis* **2001**, 783–787; (b) Heydari, A.; Larijani, H.; Emami, J.; Karami, B. *Tetrahedron Lett.* **2000**, *41*, 2471–2473.
11. Bandgar, B. P.; Shaikh, K. A. *Tetrahedron Lett.* **2003**, *44*, 1959–1961.
12. (a) Rainer, G.; Karüger, U.; Klemn, K. *Arzneim.-Forsch.* **1981**, *3*, 649–655; (b) Riedel, R. *Arzneim.-Forsch.* **1981**, *31*, 655–665; (c) Bernard, M.; Hulley, E.; Molenda, H.; Stochla, K.; Wrzeclono, U. *Pharmazie* **1986**, *41*, 56.
13. Saxena, A. S. Ph.D. Dissertation, Lucknow University, 2001; pp 57–58.
14. Typical procedure for **3**: A mixture of indole **1** (4.03 mmol) and 4-formylpyrazole **2** (2.01 mmol) in chloroform (15 mL) was stirred for 0.5–1 h in the presence of Amberlyst 15 (141 mg) at ambient temperature. The precipitate along with the catalyst was filtered off, washed with chloroform (10 mL). The solid obtained was dissolved in acetone and filtered to separate the catalyst. The filtrate was concentrated to the appropriate volume and left for crystallization. Compound **3a**: mp>260 °C, IR (KBr) $\nu = 3405$ cm^{-1} (NH); ^{1}H NMR (DMSO-d_6) 5.89 (s, 1H, CH), 6.84–7.00 (m, 5H, ArH), 7.24–7.49 (m, 10H, ArH), 7.68–7.72 (m, 3H, ArH), 7.79–7.83 (m, 2H, ArH), 8.12 (s, 1H, pyrazolyl), 10.86 (br s, 2H, NH); MS(EI) m/z 464 (M^+); Anal. Calcd for $C_{32}H_{24}N_4$: C, 82.27; H, 5.21; N, 12.06. Found: C, 82.36; H, 5.11; N, 11.95. Compound **3b**: mp 250 °C, IR (KBr) $\nu = 3407$ cm^{-1} (NH); ^{1}H NMR (Acetone-d_6) 2.34 (s, 3H, CH_3), 6.08 (s, 1H, CH), 6.89–7.28 (m, 10H, ArH), 7.36–7.47 (m, 5H, ArH), 7.69–7.83 (m, 4H, ArH), 7.99 (s, 1H, pyrazolyl), 10.16 (br s, 2H, NH); MS(EI) m/z 478 (M^+); Anal. Calcd for $C_{33}H_{26}N_4$: C, 82.82; H, 5.48; N, 11.71. Found: C, 82.68; H, 5.30; N, 11.75. Compound **3c**: mp 252 °C, IR (KBr) $\nu = 3405$ cm^{-1} (NH); ^{1}H NMR (DMSO-d_6) 3.80 (s, 3H, OCH_3), 6.07 (s, 1H, CH), 6.89–7.26 (m, 10H, ArH), 7.37–7.45 (m, 5H, ArH), 7.78–7.97 (m, 4H, ArH), 8.03 (s, 1H, pyrazolyl), 10.07 (br s, 2H, NH); MS(EI) m/z 494 (M^+); Anal. Calcd for $C_{33}H_{26}N_4O$: C, 80.14; H, 5.30; N, 11.32. Found: C, 79.96; H, 5.32; N, 11.40. Compound **3d**: mp>260 °C, IR (KBr) $\nu = 3407$ cm^{-1} (NH); ^{1}H NMR (Acetone-d_6) 5.91 (s, 1H, CH), 6.84–7.11 (m, 5H, ArH), 7.17–7.49 (m, 10H, ArH), 7.68–7.82 (m, 4H, ArH), 8.10 (s, 1H, pyrazolyl), 10.86 (br s, 2H, NH); MS(EI) m/z 482 (M^+); Anal. Calcd for $C_{32}H_{23}FN_4$: C, 79.65; H, 4.80; N, 11.61. Found: C, 79.53; H, 4.90; N, 11.42. Compound **3e**: mp>260 °C, IR (KBr) $\nu = 3410$ cm^{-1} (NH); ^{1}H NMR ($CDCl_3$) 5.93 (s, 1H, CH), 6.79–6.81 (m, 2H, ArH), 6.96–7.03 (m, 2H, ArH), 7.14–7.36 (m, 11H, ArH), 7.59–7.68 (m, 4H, ArH), 7.95 (s, 1H, pyrazolyl), 10.86 (br s, 2H, NH); MS(EI) m/z 498 (M^+); Anal. Calcd for $C_{32}H_{23}ClN_4$: C, 77.02; H, 4.65; N, 11.23. Found: C, 77.21; H, 4.70; N, 11.30. Compound **3f**: mp>260 °C, IR (KBr) $\nu = 3405$ cm^{-1} (NH); ^{1}H NMR (Acetone-d_6) 6.08 (s, 1H, CH), 6.90–7.14 (m, 5H, ArH), 7.27–7.54 (m, 10H, ArH), 7.75–7.85 (m, 4H, ArH), 8.00 (s, 1H, pyrazolyl), 10.16 (br s, 2H, NH); MS (FAB) 544 (M^++1); Anal. Calcd for $C_{32}H_{23}BrN_4$: C, 70.07; H, 4.26; N, 10.30. Found: C, 70.10; H, 4.28; N, 10.41. Compound **3g**: mp 248 °C, IR (KBr) $\nu = 3406$ cm^{-1} (NH); ^{1}H NMR (Acetone-d_6) 6.07 (s, 1H, CH), 6.83–6.91 (m, 4H, ArH), 7.02–717 (m, 6H, ArH),7.31–7.40 (m, 6H, ArH), 7.70 (d, $J = 8.38$ Hz, 2H, ArH), 7.82 (s, 1H, pyrazolyl), 10.02 (br s, 2H, NH); MS (FAB) 471 (M^++1); Anal. Calcd for $C_{30}H_{22}N_4S$: C, 76.57; H, 4.71; N, 11.91. Found: C, 76.40; H, 4.80; N, 11.80. Compound **3h**: mp>260 °C, IR (KBr) $\nu = 3411$ cm^{-1} (NH); ^{1}H NMR (Acetone-d_6) $\delta = 6.14$ (s, 1H, CH), 6.88–6.91 (m, 2H, ArH), 7.02–7.75 (m, 26H, ArH), 7.92 (s, 1H, pyrazolyl), 10.16 (br s, 2H, NH); MS (FAB) 617 (M^++1); Anal. Calcd for $C_{44}H_{32}N_4$: C, 85.69; H, 5.23; N, 9.08. Found: C, 85.70; H, 5.28; N, 9.10. Compound **3i**: mp>260 °C, IR (KBr) $\nu = 3411$ cm^{-1} (NH); ^{1}H NMR (Acetone-d_6) δ 2.24 (s, 3H, CH_3), 6.26 (s, 1H, CH), 6.81–6.90 (m, 2H, ArH), 6.93–7.05 (m, 4H, ArH), 7.17–7.20 (m, 6H, ArH), 7.36–7.46 (m, 13H, ArH), 7.60 (d, $J = 8.20$ Hz, 2H, ArH), 7.98 (s, 1H, pyrazolyl), 10.39 (br s, 2H, NH); MS (FAB) 631 (M^++1); Anal. Calcd for $C_{45}H_{34}N_4$: C, 85.68; H, 5.43; N, 8.88. Found: C, 85.80; H, 5.51; N, 8.74. Compound **3j**: mp>260 °C, IR (KBr) $\nu = 3409$ cm^{-1} (NH); ^{1}H NMR (Acetone-d_6) δ 3.76 (s, 3H, OCH_3), 6.23 (s, 1H, CH), 6.71–6.82 (m, 4H, ArH), 7.05–7.49 (m, 21H, ArH), 7.75–7.78 (m, 2H, ArH), 7.98 (s, 1H, pyrazolyl), 10.40 (br s, 2H, NH); MS (FAB) 647 (M^++1); Anal. Calcd for $C_{45}H_{34}N_4O$: C, 83.57; H, 5.30; N, 8.66. Found: C, 83.60; H, 5.41; N, 8.50. Compound **3k**: mp>260 °C, IR (KBr) $\nu = 3408$ cm^{-1} (NH); ^{1}H NMR (Acetone-d_6) δ 6.19 (s, 1H, CH), 6.78–6.91 (m, 4H, ArH), 7.02–7.12 (m, 2H, ArH), 7.18–7.50 (m, 19H, ArH), 7.78 (d, $J = 8.0$ Hz, 2H, ArH), 8.01 (s, 1H, pyrazolyl), 10.42 (br s, 2H, NH); MS (FAB) 635 (M^++1); Anal. Calcd for $C_{44}H_{31}FN_4$: C, 83.26; H, 4.92; N, 8.83. Found: C, 83.20; H, 4.96; N, 8.84. Compound **3l**: mp>260 °C; IR (KBr) $\nu = 3410$ cm^{-1} (NH); ^{1}H NMR (Acetone-d_6) 6.20 (s, 1H, CH), 6.77–6.85 (m, 2H, ArH), 7.02–7.51 (m, 23H, ArH), 7.78 (d, $J = 8.2$ Hz, 2H, ArH), 8.02 (s, 1H, pyrazolyl), 10.43 (br s, 2H, NH); MS (FAB) 651 (M^++1); Anal. Calcd for $C_{44}H_{31}ClN_4$: C, 81.15; H, 4.80; N, 8.60. Found: C, 81.20; H, 4.90; N, 8.48. Compound **3m**: mp>260 °C, IR (KBr) $\nu = 3400$ cm^{-1} (NH); ^{1}H NMR (Acetone-d_6) 6.18 (s, 1H, CH), 6.80–6.83 (m, 2H, ArH), 7.00–7.08 (m, 2H, ArH), 7.18–7.45 (m, 21H, ArH), 7.77 (d, $J = 8.20$ Hz, 2H, ArH), 8.00 (s, 1H, pyrazolyl), 10.42 (br s, 2H, NH); MS (FAB) 696 (M^++1); Anal. Calcd for $C_{44}H_{31}BrN_4$: C, 75.97; H, 4.49; N, 8.05. Found: C, 75.80; H, 4.38; N, 8.12. Typical procedure for **5**: A solution of indole **1** (3.7 mmol) and 4,4′-di(formylphenoxy)alkane **4** (0.9 mmol) in chloroform (15 mL) was stirred with Amberlyst 15 (130 mg) for 1h. The precipitate obtained was collected and purified by crystallization. Compound **5a**: mp 240 °C, IR (KBr) $\nu = 3407$ cm^{-1} (NH); ^{1}H NMR (Acetone-d_6) 4.26 (s, 4H, OCH_2), 5.80 (s, 2H, CH), 6.80–6.92 (m, 12H, ArH), 7.00–7.03 (m, 4H, ArH), 7.26 –7.40 (m, 12H, ArH), 10.81 (br s, 4H, NH); MS (FAB) 703 (M^++1); Anal. Calcd for $C_{48}H_{38}N_4O_2$: C, 82.03; H, 5.46; N, 7.97. Found: C, 82.16; H, 5.50; N, 7.82. Compound **5b**: mp 220 °C, IR (KBr) $\nu = 3407$ cm^{-1} (NH); ^{1}H NMR (DMSO-d_6) 2.24–2.27 (m, 2H, CH_2), 4.24 (t, $J = 6.20$ Hz, 4H, OCH_2), 5.94 (s, 2H, CH), 6.87–7.02 (m, 12H, ArH), 7.11–7.19 (m, 4H, ArH), 7.36–7.50 (m, 12H, ArH), 10.81 (br s, 4H, NH); MS (FAB) 717 (M^++1); Anal. Calcd for $C_{49}H_{40}N_4O_2$: C, 82.09; H, 5.62; N, 7.81. Found: C, 81.96; H, 5.54; N, 7.87.
15. X-ray crystal data of **3e:** $C_{32}H_{23}N_4Cl{\cdot}2CHCl_3$, $M = 737.73$, monoclinic, $P2_1/n$, $a = 12.246(1)$, $b = 20.729(2)$, $c = 13.366(2)$ Å, $\beta = 96.01(1)°$, $V = 3374.3(7)$ Å^3, $Z = 4$, $D_c = 1.452$ g cm^{-1}, μ (Mo-Kα)=0.62 mm^{-1}, $F(000) = 1504.0$, brown rectangular crystal, size $0.375 \times 0.150 \times 0.075$ mm, 8081 reflections measured ($R_{int} = 0.052$), 6631 unique, $R_w = 0.223$ for all data, conventional $R = 0.084$ [$(\Delta/\sigma)_{max} = 0.000$] on F values of 2548 reflections with $I > 2\sigma(I)$, $S = 1.001$ for all data and 415

parameters. Unit cell determination and intensity data collection ($2\theta = 52°$) was performed on a Bruker P4 diffractometer at 293(2) K. Structure solutions by direct methods and refinements by full-matrix least-squares methods on F^2. Programs: *XSCANS* [(Siemens Analytical X-ray Instruments Inc.: Madison, Wisconsin, USA 1996) were used for data collection and data processing], *SHELXTL-NT* [(Bruker AXS Inc.: Madison, Wisconsin, USA 1997) was used for structure determination, refinements and molecular graphics]. Further details of the crystal structure investigation can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB21EZ, UK (CCDC deposit No: 178524).

16. Braga, D.; Grepioni, F. *Acc. Chem. Res.* **2000**, *33*, 601–608.