VCl_3 catalysed efficient synthesis of bis(indolyl)methanes

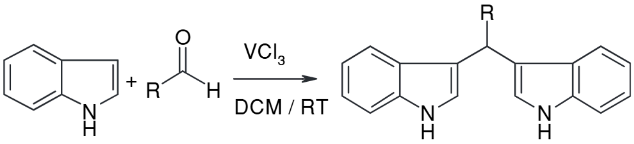
Bavanthula Rajitha*, Penthala Narsimha Reddy, Buridapad Sunil Kumar, Neeladri Sreenivasulu and Yerram Reddy Thirupathi Reddy

Department of Chemistry, National Institute of Technology, Warangal, India

VCl_3 is found to be an efficient catalysts for the electrophilic substitution reaction of indoles with aromatic aldehydes in dichloromethane to afford the corresponding bis(indolyl)methanes in excellent yields at room temperature.

Keywords*:* VCl_3, indole, aldehydes, bis(indolyl)methanes, electrophilic substitution

Indoles and their derivatives are important intermediates in organic synthesis due to their pharmacological activities.[1,2] Bis(indolyl)alkanes and their derivatives have received more attention because of their presence in bioactive metabolites and marine materials.[3] Hence, the synthesis of these moieties has become interesting targets to synthetic organic chemists and biologists. The simple method for the synthesis of this class of compounds involves the electrophilic substitution of indoles with carbonyl compounds in the presence of protic[4] or Lewis acids[5,6]. Recently $LiClO_4$[7], $In(OTf)_3$[8], I_2[9], Zeolite-HY[10] and $KHSO_4$[11] were also found to catalyse these reactions. Thus the development of efficient and versatile catalytic system for this transformation is an active ongoing research area. We now report a mild and highly efficient procedure for the synthesis of bis(indolyl)methanes using VCl_3 as catalyst at room temperature in good yields.

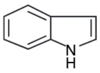
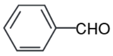
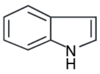
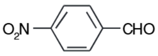
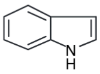
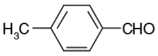
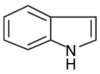
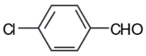
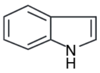
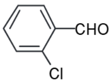
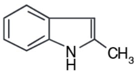
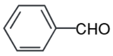
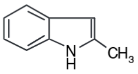
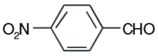
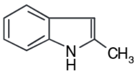
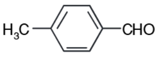
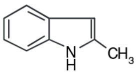
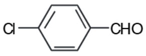
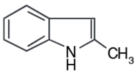
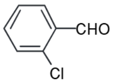
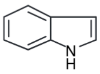
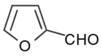


1 a–b **2 a–b** **3 a–k**

Scheme 1

Initially we have studied the electrophilic substitution reaction of benzaldehyde (2.5 mmol) with indole (5.0 mmol) using 10 mol% of VCl_3 in dichloromethane (30 ml) as solvent at room temperature (Scheme 1). The reaction is completed with in 30 min. Furthermore, the use of 10 mol% of VCl_3 in dichloromethane is sufficient to promote the reaction and no additives are required for this conversion. Encouraged by these results, several aromatic aldehydes were examined under the optimised conditions. The best results were achieved when the reactions were carried out at room temperature for 30–45 min in the presence of catalytic amounts VCl_3. The generality and scope of the reaction is summarised in Table 1.

Table 1 VCl_3 catalysed efficient synthesis of bis(indolyl)methanes[a]

Product	Indole	Aldehyde	M.p./°C	M.p./°C[b]	Time/min	Yield/%
3a			85–87	88–90[6]	30	93
3b			260–262	265–267[9]	45	95
3c			94–96	95–97[6]	30	90
3d			100-102	104–105[9]	40	92
3e			103–105	108–110[9]	30	90
3f			101–103	–	45	91
3g			239–241	240–242[9]	45	94
3h			106–108	–	40	95
3i			116–118	–	35	91
3j			122–124	–	40	93
3k			114–116	113–115[9]	45	95

[a]All products were characterised by ^1H NMR, IR, and mass spectral data. [b]Literature melting points.

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* Correspondent. E-mail: penthala_nr@yahoo.co.in

Experimental

To a stirred solution of indole (5 mmol), Benzaldehyde (2.5 mmol) in dichloromethane (30 cm^3) at room temperature was added VCl_3 (10 mol%). The mixture was maintained for 30 minutes at room temperature. After completion of the reaction as indicated by TLC, the reaction mixture was quenched with water (20 cm^3), organic layer was washed twice with 10% w/v NaCl aqueous solution (2 × 20 cm^3) and dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (ethyl acetate: hexane=2:8) to afford the product.

3f: ^{1}H NMR (200 MHz, $CDCl_3$): 2.13 (s, 6H), 6.12 (s, 1H), 6.72–6.93 (m, 7H), 7.21 (d, 2H, *J*=8.17Hz), 7.44 (d, 2H, *J*=8.17 Hz), 8.12 (d, 2H, *J*=8.20 Hz), 8.25 (brs, 2H, NH). EIMS: *m/z* (%): 350 (35, M$^+$), 349 (100, M$^+$-1). Calculated. C, 85.68, H, 6.33, N, 7.99%. Found. C, 85.88, H, 6.46, N, 7.69%.

3h: ^{1}H NMR (200 MHz, $CDCl_3$): 2.10 (s, 6H), 2.26 (s, 3H), 6.20 (s, 1H), 6.62–6.96 (m, 8H), 7.53 (d, 2H, *J*=8.20 Hz), 7.89 (brs, 2H, NH), 8.0 (d, 2H, *J*=8.20 Hz). EIMS: *m/z* (%): 364 (32, M$^+$), 363 (100, M$^+$-1). Calculated. C, 85.68, H, 6.64, N, 7.69%. Found. C, 85.63, H, 6.62, N, 7.65%.

3I: ^{1}H NMR (200 MHz, $CDCl_3$): 2.21 (s, 6H), 6.34 (s, 1H), 6.62–6.89 (m, 6H), 7.33 (d, 2H, *J*=8.10 Hz), 7.65 (d, 2H, *J*=8.17 Hz), 8.10 (d, 2H, *J*=8.10 Hz), 8.35 (brs, 2H, NH). EIMS: *m/z* (%): 384 (40, M$^+$), 383 (100, M$^+$-1). Calculated. C, 78.01, H, 5.50, Cl, 9.21, N, 7.28%, Found. C, 78.11, H, 5.56, Cl, 9.26, N, 7.18%.

3j: ^{1}H NMR (200 MHz, $CDCl_3$): 2.12 (s, 6H), 6.25 (s, 1H), 6.62–6.83 (m, 6H), 7.28(d, 2H, *J*=8.15 Hz), 7.52 (d, 2H, *J*=8.17Hz), 8.20 (brs, 2H, NH), 8.38 (d, 2H, *J*=8.2 Hz). EIMS: *m/z* (%): 384 (36, M$^+$), 383 (100, M$^+$-1). Calculated. C, 78.01, H, 5.50, Cl, 9.21, N, 7.28%, Found. C, 78.06, H, 5.59, Cl, 9.17, N, 7.24%.

Conclusion

In conclusion we have developed an efficient electrophilic substitution reaction of indoles with various aromatic aldehydes by using VCl_3 as catalyst. The method offers several advantages including high yields, short reaction times and a simple experimental work-up procedure and product isolation; hence, it is a useful addition to the existing methods.

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