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Gallium(III) halide-catalyzed coupling of indoles with phenylacetylene: synthesis of bis(indolyl)phenylethanes☆

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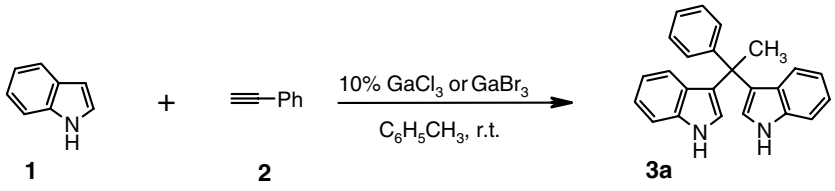
Abstract—Indoles undergo smooth coupling with phenylacetylene in the presence of 10 mol% of gallium(III) chloride or gallium(III) bromide under mild conditions to afford the corresponding 1,1-bis(1*H*-3-indolyl)-1-phenylethanes in high yields and with high selectivity.

The bis(indolyl)alkane moiety is present in various natural products possessing important biological activity.[1,2] Therefore, a number of synthetic methods for the preparation of bis(indolyl)alkane derivatives have been reported in the literature by reacting indoles with various aldehydes and ketones in the presence of either a Lewis acid[3] or a protic acid.[4] Metal triflates such as $Dy(OTf)_3$/ionic liquid and molecular iodine have also been employed for the synthesis of bis(indolyl)alkanes by reacting indoles with aldehydes and ketones.[5] Therefore, the development of simple and convenient procedures for the synthesis of bis(indolyl)phenylethane continue to be a challenging endeavour in synthetic organic chemistry. Recently, there has been considerable interest in gallium-mediated transformations.[6] Due to their unique catalytic properties, gallium halides have been used widely for a variety of organic transformations.[7] In particular, gallium(III) compounds are utilized as effective Lewis acids to activate alkynes under extremely mild conditions.[8] However, there have been no reports on the use of gallium(III) halides as catalysts for the synthesis of biologically active natural products containing the bis(indolyl)phenylethane moiety via the coupling of indoles with phenyl acetylene.[9]

In this article, we disclose a mild and efficient method for the preparation of bis(indolyl)phenylethanes from indoles and phenylacetylene using 10% gallium(III) halide as the novel catalyst. Initially, we attempted the coupling of indole, **1** (2 equiv) with phenylacetylene, **2** (1.2 equiv) in the presence of 10 mol% of gallium(III) chloride and gallium(III) bromide. The reaction went to completion in 6 h and the product was obtained in 86% yield (**3a**, Scheme 1).

Encouraged by this result, we turned our attention to various substituted indoles. Several substituted indoles such as *N*-methyl-, *N*-ethyl-, 2-methyl-, 4-nitro-, 4-bromo-, 5-cyano- and 7-ethyl-indoles underwent smooth coupling with phenylacetylene to afford the



Scheme 1.

Keywords: Gallium(III) compounds; Phenylacetylenes; Indoles; Bis(indolyl)phenylethanes.
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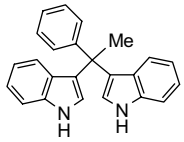
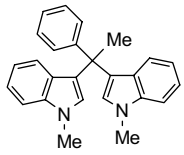
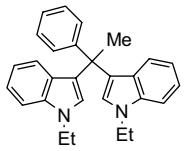
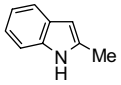
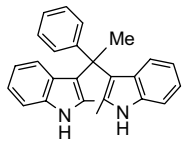
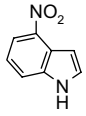
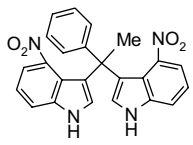
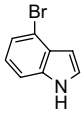
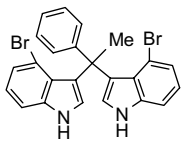
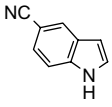
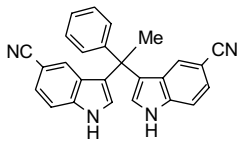
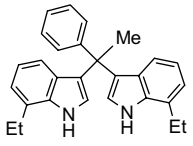
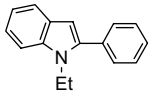
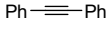
corresponding bis(indolyl)phenylethanes (Table 1, entries **3b–h**). In all cases, the reactions proceeded smoothly at room temperature with high efficiency. However, 1-ethyl-2-phenyl indole did not react with phenylacetylene in the presence of 10 mol% of gallium(III) halide (Table 1, entry **i**). Furthermore, diphenylacetylene and alkyl-substituted alkynes such as *n*-octyne failed to produce the desired products even on heating under reflux (Table 1, entries **j** and **k**), because of their intrinsically lower reactivity in comparison to

Table 1. Gallium(III) chloride coupling of indoles with phenyl acetylene

Entry	Indoles **1**	Alkynes **2**	Product[a] **3**	Time (h)	Yield (%)[b]
a				6.0	86
b				8.0	75
c				6.5	84
d				7.5	80
e				6.0	82
f				6.5	88
g				7.0	83
h				6.0	85
i			No reaction	30.0	—
j			No reaction	23.0	—
k			No reaction	24.0	—

[a] All products were characterized by ^{1}H NMR, IR and mass spectrometry.
[b] Yield refers to the isolated pure products after column chromatography.

phenyl acetylene. In the absence of catalyst, no reaction was observed. As solvent, toluene appeared to give the best results. Among the various Lewis acids such as $InCl_3$, $InBr_3$, InI_3, YCl_3 and $BiCl_3$ tested, gallium trihalides were found to be the most effective for this conversion. $In(OTf)_3$ (20 mol%) was also worked well to afford the corresponding bis(indolyl)phenylethane in 12 h under reflux. The scope and generality of this process is illustrated with respect to various indoles and the results are presented in Table 1.

In summary we have described a simple, convenient and efficient protocol for the synthesis of bis(indolyl)phenylethanes from indoles and phenylacetylene using 10 mol% of GaX_3 as catalyst. $GaCl_3$ and $GaBr_3$ are solid and stable to air or moisture and are easy to handle even on multi-gram scales and are found to activate alkynes very effectively under mild conditions. This process offers several advantages such as high conversions, high selectivity, experimental simplicity and high catalytic activity, which makes it a useful and attractive strategy for the preparation of bis(indolyl)phenylethanes in a single step operation.

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9. A mixture of phenylacetylene (1.2 mmol), indole (2 mmol), gallium trihalide (0.10 mmol) in toluene (10 mL) was stirred at room temperature for the appropriate time (see Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was diluted with water and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1.5:8.5) to afford the pure bis(indolyl)phenylethane. Spectroscopic data for selected products: **3e**: 4-Nitro-3-[1-{4-nitro-1*H*-3-indolyl}-1-phenylethyl]-1*H*-indole: yellow solid, mp = 283–286 °C. IR (KBr): ν_{max}: 3436, 2983, 1740, 1532, 1468, 1376, 1331, 1242, 1046, 786 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 11.32 (br s, 2H, NH), 7.98 (s, 2H), 7.90 (d, J = 9.2 Hz, 2H), 7.44 (d, J = 9.2 Hz, 2H), 7.35–7.22 (m, 5H), 6.96 (s, 2H), 2.36 (s, 3H). FAB Mass: *m/z* (%): 427 (M+1, 35), 411 (55), 349 (12), 313 (5), 289 (5), 265 (40), 219 (8), 191 (5), 154 (18),123 (10), 109 (8), 95 (35), 81 (40), 69 (65), 57 (100). HRMS calcd for $C_{24}H_{19}N_4O_4$: 427.1406. Found: 427.1413 (M+1). **3f**: 4-Bromo-3-[1-4-bromo-1*H*-3-indolyl-1-phenylethyl]-1*H*-indole: brown solid, mp = 216–220 °C. IR (KBr): ν_{max}: 3432, 2982, 1723, 1562, 1456, 1410, 1374, 1330, 1217, 1102, 1050, 881, 767, 702, 666, 584 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.90 (br s, 2H, NH), 7.38–7.20 (m, 11H), 6.60 (d, J = 6.5 Hz, 2H), 2.30 (s, 3H). FAB Mass: *m/z* (%): 494 (M^+, 30), 479 (45), 399 (8), 391 (10), 298 (30), 279 (5), 219 (8), 204 (5), 191 (5), 167 (12), 154 (50), 136 (40), 115 (15), 95 (45), 81 (48), 69 (60), 57 (100). HRMS calcd for $C_{24}H_{19}N_2Br_2$: 492.9914. Found: 492.9923 (M+1). **3g**: 3-[1-(5-cyano-1*H*-3-indolyl)-1-phenylethyl]-1*H*-5-indolecarbonitrile: yellowish solid, mp = 192–194 °C. IR (KBr): ν_{max}: 3418, 2885, 2823, 2254, 2215, 2127, 1645, 1475, 1378, 1339, 1243, 1103, 1026, 1004, 824, 763, 623 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 11.22 (br s, 2H, NH), 7.48 (d, J = 8.4 Hz, 2H), 7.39 (s, 2H), 7.30–7.22 (m, 7H), 6.82 (s, 2H), 2.30 (s, 3H). EIMS: *m/z* (%): 386 (M^+, 40), 372 (100), 309 (10), 229 (12), 185 (7), 140 (5). HRMS calcd for $C_{26}H_{18}N_4$: 386.1531. Found: 386.1525.