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Novel gallium-mediated C3-allylation of indoles and pyrroles in aqueous media promoted by Bu_4NBr

Dipak Prajapati,* Mukut Gohain and Baikuntha J. Gogoi

Medicinal Chemistry Division, Regional Research Laboratory, Jorhat 785 006, Assam, India

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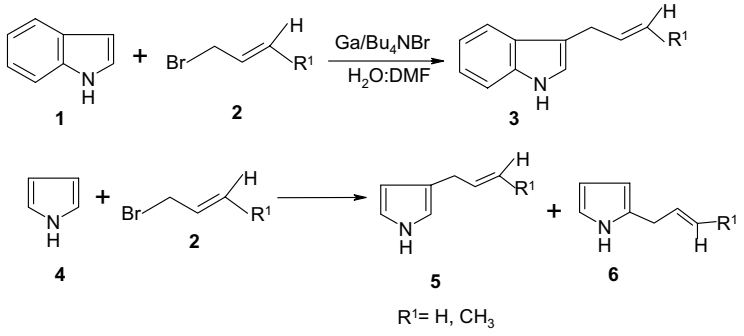
Abstract—A mild and efficient protocol for the coupling of indoles and pyrroles with allyl halides such as allyl bromide, crotyl bromide and propargyl bromide in the presence of gallium metal in a Bu_4NBr–DMF–H_2O system has been developed. The reaction is equally effective when cadmium is used in lieu of gallium and the corresponding 3-allyl indoles and 3-allyl pyrroles were obtained in almost comparable yields.

The recent interest in aqueous medium metal-mediated carbon–carbon bond formation led to the continuing search for more reactive and selective metal mediators for such reactions.[1,2] The study and application of Barbier–Grignard type reactions[3] in aqueous media is still in its infancy, and the full synthetic potential of such reactions is waiting to be explored and needs to be expanded.[4] The application of the Grignard reaction in carbon–carbon bond forming reactions for large scale industrial application is limited[5] by the expense of the metal, the anhydrous ether solvent required and complications involved in the waste solvent disposal. Among such reactions, allylation of carbonyl compounds to give homoallylic alcohols has received the much attention.[6] Metals such as tin,[7] zinc,[8] indium[9] and magnesium[10] have been found to be effective for such transformations. Metals that rapidly form an oxide shell would not be suitable for mediating nucleophilic addition. When one looks at the reduction potentials of various metals as well as their reactivity towards water, gallium emerges as a promising candidate.[11] There have been only a few examples of synthetic reactions using gallium,[12] which belongs to the same group as the extensively studied boron, aluminium and indium[13] metals. Previously, indium has been used for allylations in aprotic solvents.[14] After comparing the first ionization and reduction potentials of gallium with those of indium (Ga: FIP, 5.99 eV, E°, $Ga^{+3}/Ga = -0.56$ V; In: FIP, 5.79 eV, E°, $In^{+3}/In = -0.345$ V), Wang et al.[15] predicted similar properties for these two metals. As in



Scheme 1.

Keywords: Gallium; Cadmium; Aqueous media.
* Corresponding author. Tel.: +91 376 2370356; fax: +91 376 2370115; e-mail: dr_dprajapati2003@yahoo.co.uk

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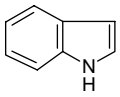
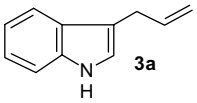
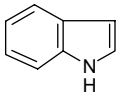
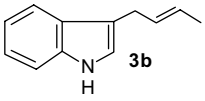
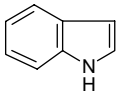
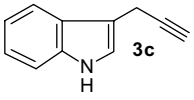
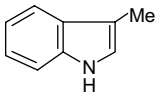
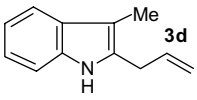
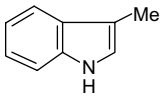
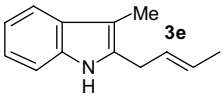
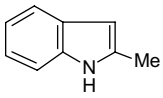
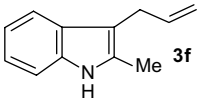
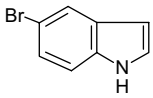
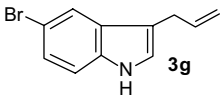
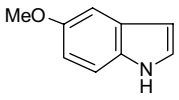
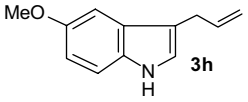
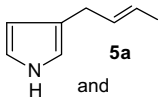
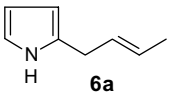
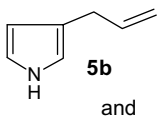
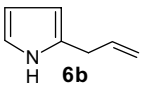
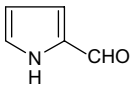
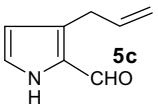
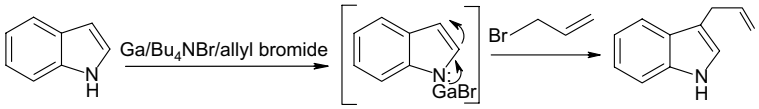
the case of indium, the reduction potential of gallium is not too negative, and thus it is not sensitive to water and does not form oxides readily in air. In continuation of our on-going programme on metal-mediated organic transformations,[16] we report herein the first example of gallium-mediated C3-allylation of indoles and pyrroles under aqueous conditions using tetrabutylammonium bromide (Bu_4NBr) as an additive (Scheme 1). Some very recent reports using metallic zinc[17] and Pd/triethylborane[18] for the alkylation of indoles encouraged us to report our results on C3-allyation of indoles and pyrroles. The reaction proceeded efficiently at ambient

Table 1. Gallium mediated allyation of indoles and pyrroles

Entry	Substrate **1**, **4**	Allyl halide **2**	Product	Reaction time (h) Ga	Yield[a] (%) Ga	Reaction time (h) Cd	Yield[a] (%) Cd
1			 **3a**	4.5	80	6.0	76
2			 **3b**	4.0	80	6.5	75
3			 **3c**	5.0	75	7.0	73
4			 **3d**	10.0	70	12	65
5			 **3e**	9.0	75	10	70
6			 **3f**	6.0	70	8.0	70
7			 **3g**	6.0	70	8.5	65
8			 **3h**	6.0	73	8.5	70
9			 **5a** and  **6a**	6.5	70 15	8.0	65
10			 **5b** and  **6b**	7.0	75 12	8.0	60
11			 **5c**	7.0	65	12	63

[a] Isolated yields.



Scheme 2.

temperature and pressure and the corresponding allylic compounds were obtained in high yields.

There is considerable interest in indoles possessing substituents at the 3-position due to their numerous biological activities.[19] Regioselective allylic alkylation at the 3-position of indoles lends itself to an efficient and straightforward method for the synthesis of many naturally occurring indole alkaloids.[20] A variety of methods have been reported for the preparation of 3-substituted indoles.[21] Of these, the Mannich[22] and Vilsmeier–Haack[23] syntheses are used most extensively.[24] Allylation at the 3-position is involved in a total synthesis of a calabar bean alkaloid, (−)-physovenine.[25]

When indole was reacted with the allylgallium reagent (generated in situ) (1:1) in a Bu_4NBr–DMF–H_2O system, followed by preparative TLC, an 80% yield of the allylated indole **3a** was obtained. The structure of **3a** was confirmed by high resolution spectral analysis. The coupling also proceeded effectively when crotylgallium or propargylgallium reagents were used and the corresponding 3-alkylindole derivatives **3b** and **3c** were obtained in high yields. The reactions were clean and no trace of side products could be detected in the NMR spectra of the crude products. All the products were characterized by infrared and ^1H NMR spectroscopy and finally by comparing with authentic samples.[17,18] The scope and efficiency of this method are summarized in Table 1. From the results it is clear that substitution on the indole nucleus occurred exclusively at the 3-position. Also, when 3-methylindole or 2-methylindole were examined, the reaction proceeded effectively at the 2- and 3-positions, respectively. However, with *N*-methylindole the reaction did not proceed at all under similar conditions, which means that the method is only suitable for the allylation of N-unprotected indoles.

Subsequently, we investigated the allylation of pyrroles, which are important intermediates not only for the synthesis of drugs and pharmaceuticals but also for the development of organic functional materials.[26] In general, pyrroles have rather weak nucleophilicity compared with indoles and also show a lability to acidic conditions. When the allylgallium reagents were treated with pyrrole under aqueous conditions, the corresponding 3-allylpyrrole derivatives were obtained in 70–75% yields along with 2-allylpyrroles in 12–15% yields. Yields were improved marginally and the reaction time could be reduced by 1 h in the presence of 0.1 equiv of sodium iodide along with TBAB. However, with 2-substituted pyrroles such as 2-formylpyrrole the corresponding 3-allylated pyrrole was obtained in 65% yield, without reaction at the carbonyl group. This is in contrast to an earlier report,[27] wherein an aldehyde group was allylated with allylbromide in a Bu_4NBr/Cd/THF–H_2O system and the corresponding homoallylic alcohols were obtained in good yields. Further, with *N*-methylpyrrole the reaction did not proceed at all.

The effect of Bu_4NBr was found to be remarkable with virtually no allylation occurring in its absence. We investigated a number of alkaline metal salts to activate the metal, such as KBr and $MgBr_2$ in place of Bu_4NBr, but found these to be ineffective, giving no reaction. Roughly 0.3 equiv of Bu_4NBr was found to be sufficient; the use of a large excess did not result in higher yields or better reaction rates. We thus used Bu_4NBr as the standard additive to activate commercial gallium metal and examined its reaction with a number of pyrroles and indoles.[28] The results summarized in the Table 1 reveal the generality of this methodology in terms of structural variations of the allyl halide moiety and in each case allylated products were isolated in high yields within 4–10 h (entries 1–10). Allyl iodide was found to be as reactive as allyl bromide, but the reactivity of allyl chloride was found to be much less. It is interesting to note that the nature of the solvent controlled the formation of allylated products. The reaction was not effective, and various by-products were formed, when acetonitrile or THF was used as the solvent. Also no isolable product was formed when the reaction was run in water alone. After screening the reaction conditions, the optimum solvent for the coupling reaction was found to be a (3:1) mixture of DMF–H_2O. Moreover, when gallium was replaced by inexpensive cadmium powder the coupling proceeded effectively and the corresponding 3-allylic pyrroles or indoles were obtained in almost comparable yields. In most cases, the reaction was complete within 4–10 h with gallium, while the reaction took a little longer with cadmium. Increasing the reaction time further gave no improvement in yield but rather led to the formation of by-products.

Although the detailed mechanism of the reaction is not clear at this stage it is likely that Bu_4NBr initiates the generation of an active allylgallium or allylcadmium reagent, which effects the formation of an indole or pyrrole Grignard-type complex that in turn reacts with allyl bromide to afford the allylated products (Scheme 2).

In conclusion, this simple and easily reproducible technique using gallium or cadmium under aqueous conditions affords various allylated products of potentially high synthetic utility in excellent yields and without the formation of any undesirable side products.

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28. In a typical procedure, a mixture of gallium powder (3 mmol, 0.207 g), allyl bromide (6 mmol, 0.730 g), Bu_4NBr (1 mmol, 0.322 g) and indole (3 mmol, 0.354 g) were taken up in DMF–H_2O (15 ml; 3:1) in a 100 ml round-bottom flask and the mixture stirred at room temperature until the completion of the reaction (TLC). After completion (4–10 h), the reaction mixture was quenched with a concentrated solution of NH_4Cl, followed by extraction with ether (3×20 ml). The combined ether extracts were washed with brine, dried over anhydrous sodium sulfate and the residue obtained on evaporation of the solvent was purified by chromatography using ethyl acetate–hexane (1:9) to afford the pure allylated product **3a** in 80% yield. 3-Allylindole **3a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.30 (dd, $J = 1.8$, 10.4 Hz, 2H), 5.25–5.55 (m, 2H), 5.85 (m, 1H), 6.65 (d, $J = 2.2$ Hz, 1H), 7.10–7.22 (m, 2H), 7.32 (d, $J = 8.3$ Hz, 1H), 7.62 (d, $J = 8.3$ Hz, 1H), 7.95 (br, 1H, NH). IR (KBr) 3400, 2920, 1460 cm^{-1}. EIMS *m*/*z* 157 $M^{+\cdot}$. Anal Calcd for $C_{11}H_{11}N$: C, 84.08; H, 7.01; N, 8.91. Found: C, 84.16; H, 7.11; N, 8.86. Similarly, other indoles, and pyrroles were reacted with allylgallium reagent to give the corresponding 3-allylated products in high yields. The reactions are generally clean and no trace of side products could be detected in the NMR spectra of the crude products. Compound **3c**: ^{1}H NMR (100 MHz, $CDCl_3$) δ 2.46 (t, $J = 2.2$ Hz, 1H), 3.18 (dd, $J = 2.2$, 6.3 Hz, 2H), 6.76 (d, $J = 2.2$ Hz, 1H), 6.98–7.12 (m, 2H), 7.28 (d, $J = 8.1$ Hz, 1H), 7.56 (d, $J = 8.1$ Hz, 1H), 8.02 (br, 1H, NH). Anal Calcd for $C_{11}H_9N$: C, 85.16; H, 5.80; N, 9.03. Found: C, 85.10; H, 5.72; N, 9.11. Compound **3g**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.90 (br, d, $J = 6.4$ Hz, 2H), 5.02–5.18 (m, 2H), 6.12–6.28 (m, 1H), 6.96 (d, $J = 7.8$ Hz, 1H), 7.06 (br, s, 1H), 7.24 (d, $J = 7.2$ Hz, 1H), 7.32 (d, $J = 7.2$ Hz, 1H), 8.12 (br, 1H, NH). IR (KBr) 3420, 1615, 1425 cm^{-1}. EIMS *m*/*z* 236 $M^{+\cdot}$. Anal Calcd for

$C_{11}H_{10}NBr$: C, 55.93; H, 4.24; N, 5.93. Found: C, 56.02; H, 4.18; N, 5.89. Compound **5a**: ^{1}H NMR (200 MHz, $CDCl_3$), δ 1.80 (d, $J = 6.0$ Hz, 3H), 3.42 (dd, $J = 1.7$, 10.4 Hz, 2H), 5.10–5.27 (m, 2H), 6.15 (d, $J = 2.5$ Hz, 1H), 6.65 (m, 1H), 6.72 (dd, $J = 2.5$, 5.5 Hz, 1H), 7.98 (br, 1H, NH). Anal. Calcd for $C_8H_{11}N$: C, 79.33; H, 9.09; N, 11.57. Found: C, 79.41; H, 9.01; N,11.64. Compound **6a**: 1.75 (d, $J = 6.5$ Hz, 3H), 3.40 (dd, $J = 1.7$, 10.4 Hz, 2H), 5.12–5.28 (m, 1H), 5.80 (m, 1H), 5.85–5.95 (m, 1H), 6.12 (dd, $J = 2.5$, 5.5 Hz, 1H), 6.70 (d, $J = 2.5$, Hz, 1H), 8.02 (br, 1H, NH). Compound **5c**: ^{1}H NMR (100 MHz, $CDCl_3$), δ 3.52 (dd, $J = 1.4$, 6.5 Hz, 2H), 4.85–5.06 (m, 2H), 5.95–6.12 (m, 1H), 6.25 (d, $J = 2.5$ Hz, 1H), 6.78 (m, 1H), 7.86 (br, 1H, NH), 9.12 (s, 1H, CHO). Anal. Calcd for C_8H_9NO: C, 71.11; H, 6.67; N, 10.37. Found: C, 71.19; H, 6.58; N, 10.44. The reaction with cadmium was carried out similarly and the corresponding products were isolated in comparable yields. Known products were characterized by comparing their spectral data with authentic samples.[17,18]