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Condensation of propargylic alcohols with indoles and carbazole in $[bmim][PF_6]/Bi(NO_3)_3{\cdot}5H_2O$: a simple high yielding propargylation method with recycling and reuse of the ionic liquid

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ABSTRACT

Propargylation of a variety of substituted indoles as well as mono- and di-propargylation of carbazole are achieved in 80–94% isolated yields by employing catalytic amounts (10 mol %) of the readily available $Bi(NO_3)_3{\cdot}5H_2O$ in $[bmim][PF_6]$ ionic liquid (IL), with repeated recycling and reuse of the IL.

Owing to the importance of the indole moiety as a building block of natural products, pharmaceuticals, and functional materials, significant research efforts have been focused in recent years to develop mild and selective synthetic routes to functionalized indoles.[1,2] The carbazole moiety represents another significant heterocyclic building block in natural products that has also been applied extensively in organic materials.[3,4]

Development of mild and selective methods for the direct introduction of propagylic groups into indoles and carbazoles is a desirable synthetic goal, thus allowing further elaboration of these intermediates. To date a limited number of methods for direct indole and carbazole propargylation have been reported, and no examples for dipropargylated carbazole appear to exist.[5–10]

Focusing on earlier studies on indoles, in the context of their work on ruthenium-catalyzed propargylation of aromatics, Uemura and associates[5] propargylated the parent indole with 1-phenylpropyne-1-ol in DCE solvent in 52% yield. Since then several other studies by other research groups have been reported that employed $CeCl_3/MeNO2$,[6a] $Ce(OTf)_3/MeNO_2$,[6b] $FeCl_3/MeNO_2$,[7] $Sc(OTf)_3/DCE$,[8] $InBr_3/DCE$,[9] and TfOH or PTSA in MeCN or $MeNO_2$.[10]

In relation to our recent studies focusing on the generation and synthetic application of propargylic cations,[11] and in continuation of our work on electrophilic chemistry in ionic liquids as solvent and catalysts,[12] we report here on a facile, high yielding direct propargylation method using propargyl alcohols **2a**, **2b**, and **2c** with a host of substituted indoles, and on mono- and dipropargylation of carbazole with **2a**, employing the readily available bismuth nitrate pentahydrate as promoter in $[bmim][PF_6]$ solvent (Figs. 1–3).[13]

The results are summarized in Table 1, entries 1–7 show the scope of the reaction for substituted indoles with propargylic alcohol **2a**, with isolated yields in 80–94% range, employing very mild conditions, and short reaction times. It is noteworthy that runs 2–7 employed recycled/reused IL,[14] and exhibit a gradual decrease in isolated yields from 94% to 81%.

Under the present reaction conditions 4-phenyl-3-butyn-2-ol failed to undergo condensation with indoles. Whereas stabilization of an α-phenyl group seems necessary for the generation of an incipient propargylic carbocation in this method, nature of the substituent at the alkynyl moiety is less critical. Thus propargylic alcohols **2b** and **2c** were successfully used in this study for the propargylation of substituted indoles (Fig. 2) to give compounds **10**–**15** in respectable isolated yields. Once again, the IL was recycled and reused in subsequent reactions without a notable decrease in the conversions.

The present method is also applicable to the propargylation of carbazole (Fig. 3), to furnish the mono- and dipropargylated derivatives by using 1.0 and 2.2 equiv of **2a**, respectively, (compounds **17** and **18**). Compound **18** was obtained as a single isomer (NMR).

In summary the present study has demonstrated the utility of $Bi(NO_3)_3{\cdot}5H_2O$ as a mild and selective Lewis acid for the propargylation

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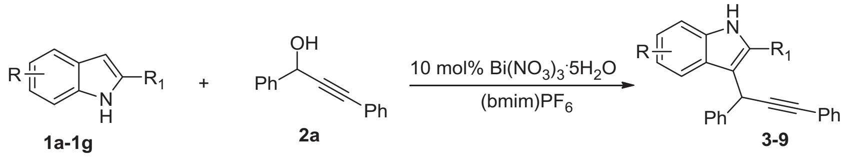


Figure 1. Propargylation of indoles with **2a** in $[bmim][PF_6]/Bi(NO_3)_3{\cdot}5H_2O$ system.

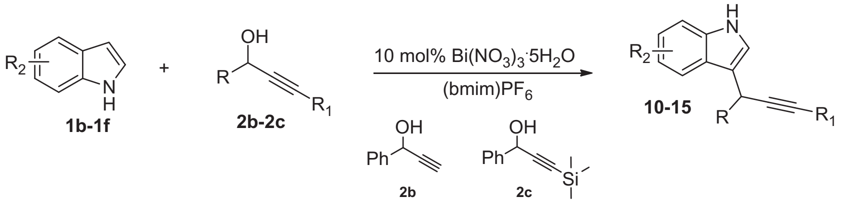


Figure 2. Propargylation of indoles with **2b** and **2c** in $[bmim][PF_6]/Bi(NO_3)_3{\cdot}5H_2O$ system.

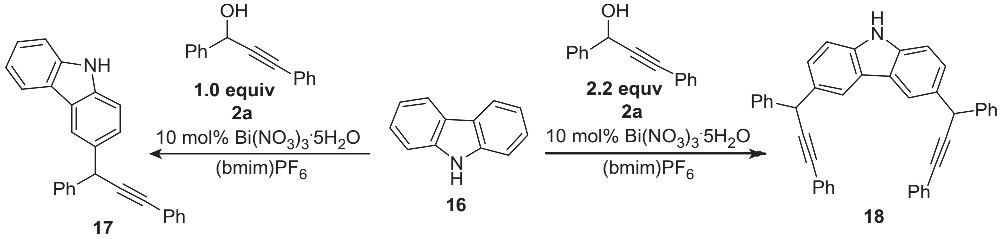
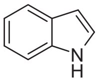
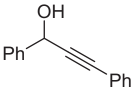
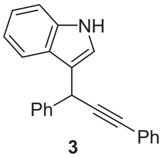
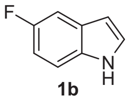
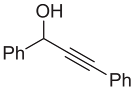
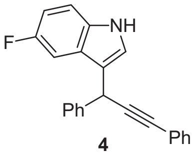
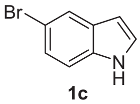
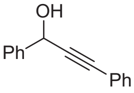
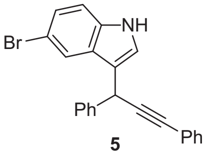
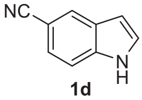
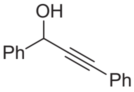
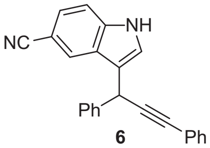
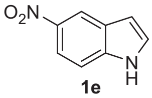
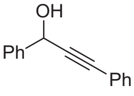
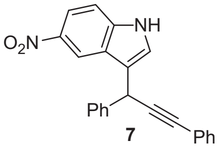


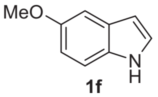
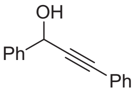
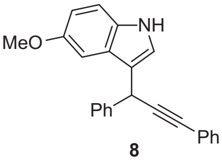
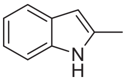
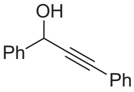
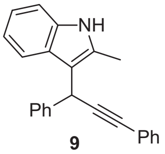
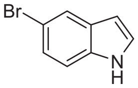
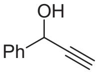
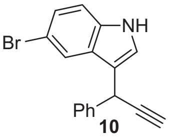
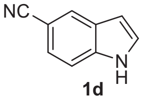
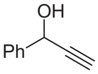
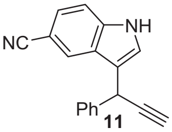
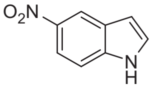
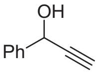
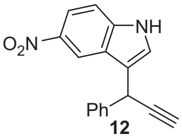
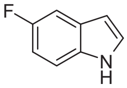
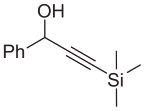
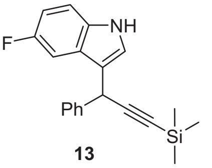
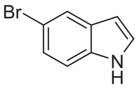
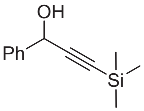
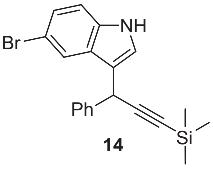
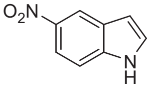
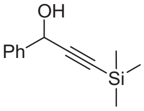
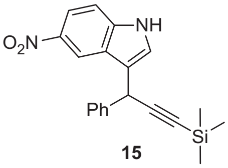
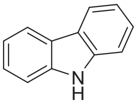
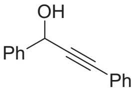
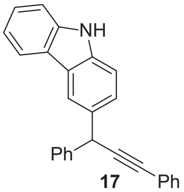
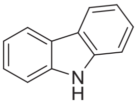
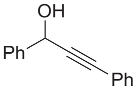
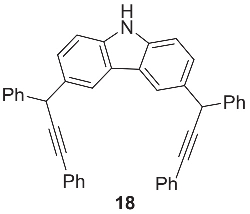
Figure 3. Propargylation of carbazole with **2a** in $[bmim][PF_6]/Bi(NO_3)_3{\cdot}5H_2O$ system.

Table 1
Propargylation of indoles and carbazole with $Bi(NO_3)_3$ $5H_2O$ in $[bmim][PF_6]$[a,b]

Entry	Indoles and Carbazole	Alcohols	Products	Temp (°C)	Time (h)	Isolated yield (%)
1	 **1a**	 **2a**	 **3**	35	3	92
2	 **1b**	 **2a**	 **4**	40	4	94
3	 **1c**	 **2a**	 **5**	40	4	91
4	 **1d**	 **2a**	 **6**	35	3	88
5	 **1e**	 **2a**	 **7**	40	5	87

(*continued on next page*)

Table 1 (*continued*)

Entry	Indoles and Carbazole	Alcohols	Products	Temp (°C)	Time (h)	Isolated yield (%)
6	 **1f**	 **2a**	 **8**	50	4	80
7	 **1g**	 **2a**	 **9**	45	4	81
8	 **1c**	 **2b**	 **10**	60	8	86
9	 **1d**	 **2b**	 **11**	55	6	89
10	 **1e**	 **2b**	 **12**	60	8	90
11	 **1b**	 **2c**	 **13**	35	2	91
12	 **1c**	 **2c**	 **14**	35	2.5	89
13	 **1e**	 **2c**	 **15**	45	3.5	86
14	 **16**	 **2a**	 **17**	50	4	84
15[c]	 **16**	 **2a**	 **18**	60	6	90

[a] Fresh [bmim]$[PF_6]$ was used in runs 1, 8, 11 and 14, whereas recycled IL was used in others.

[b] The [bmim]$[PF_6]$ could be reused without purification for up to three runs, after which it was purified and reused (see SI file).

[c] 2.2 equiv of propargylic alcohol.

of indoles and carbazole. When used in catalytic amounts, it can be dissolved in [bmim][PF_6] upon sonication to form an embedded catalyst for propargylation of indole and carbazole with propargyl alcohols. With mild reaction conditions and respectable isolated yields, coupled to recycling and reuse of the IL, the reported method has the potential to be used widely.

Acknowledgements

We thank the University of North Florida for support and Dr. Nelson Zhao of this department for NMR assistance.

Supplementary data

Supplementary data (multinuclear NMR (^{1}H, ^{13}C, ^{15}N, ^{19}F) and other characterization data are furnished for the new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.04.026.

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13. *General procedure for propargylation of indoles and carbazole*: The ionic liquid (3.5–4.0 mL) was charged into an oven-dried Schlenk tube under a nitrogen atmosphere and $Bi(NO_3)_3{\cdot}5H_2O$ (10 mol %) was added and upon sonication (for about 15 min) was dissolved in the IL. The respective indoles (1 mmol) or carbazole (1 mmol) was then introduced into the Schlenk tube under a nitrogen atmosphere followed by the desired propargylic alcohol (1 mmol). The reaction mixture was magnetically stirred, initially at rt for about 10 min followed by stirring in a pre-heated oil bath at 35–60 °C (as specified; refer to Tables 1), until completion (as monitored by TLC). Once the reaction was over, the contents were cooled to rt and extracted with dry diethyl ether or with EtOAc/Hexane (2:3 vol/vol in the case of 5-nitro and 5-cyano indole derivatives), until the final extraction did not show a spot corresponding to the starting material or to the product. The combined organic extracts were washed with DI water, dried with $MgSO_4$, and concentrated to give the crude product, which upon purification through column chromatography furnished the desired products.
14. *Re-use and recycling of IL*: After extraction, the ionic liquid was dried under high-vacuum at 60–70 °C for about 6 h and re-used in successive runs.