Cation-exchange Resin as Efficient, Cost-effective and Recyclable Catalyst for the Synthesis of 3-Propargylindoles

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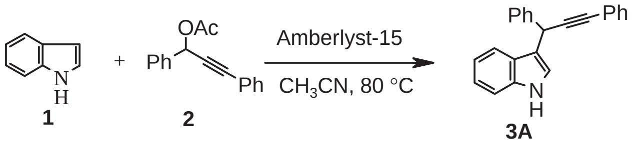
Indoles undergo smooth alkylation with propargylic acetates in the presence of Amberlyst A-15® under mild conditions to produce 3-propargylated indoles in excellent yields with high selectivity. This is the first example for the alkylation of indoles with propargylic acetates using the acid catalyst.

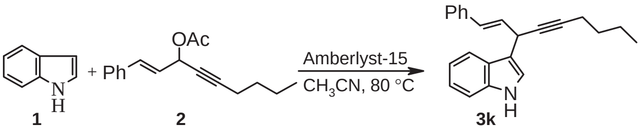
Indole derivatives are found abundantly in nature and are known to exhibit potent physiological properties.[1] Consequently, the reactions of indole and its derivatives have attracted great importance in organic synthesis.[2,3] Propargylic acetates (2-propynyl acetates) are well-known carbon electrophiles capable of reacting with various nucleophiles and their ability to undergo nucleophilic substitution reactions contributes largely to their synthetic value.[4] However, there have been no examples of the C-alkylation of indoles with propargylic acetates. However, there have been no reports on propargylation of indoles with propargylic acetates. In recent years, the use of heterogeneous catalysts such as ion-exchange resins, clay, and zeolites has received great attention in different areas of organic synthesis because of their simplicity in operation, environmental compatibility, reusability, greater selectivity, non-corrosiveness, and ready availability of the reagents at low cost.[5] Particularly, ion-exchange resins make the reaction processes quite simple, more convenient, economic, and environmentally benign which enable them to function as efficient catalysts for various transformations.[6]

In continuation of our interest on the use of solid acid catalysts,[7] herein, we report for the first time an efficient alkylation of indoles with propargylic acetates using a cheap and commercially available solid acid, Amberlyst-15®. Initially, we have attempted the alkylation of indole (**1**) with 1,3-diphenyl-2-propynyl acetate (**2**) in the presence of Amberlyst-15®. The reaction went to completion within 30 min and the product (**3A**) was obtained in 91% yield (Scheme 1).

Encouraged by the results obtained from indole and 1,3-diphenyl-2-propynyl acetate, we turned our attention to various indoles and propargylic acetates. Interestingly, substituted indoles such as 5-bromo-, 5-nitro-, 2-methyl-, and 5-methoxy carbonyl derivatives reacted well with 1,3-diphenyl-2-propynyl acetate to give the corresponding 3-propargylated indoles in excellent yields (Entries **B**–**E**, Table 1). Other propargylic acetates such as 1-(4-methylphenyl)-2-heptynyl acetate reacted efficiently with simple indole, 5-bromo indole and 7-ethyl indole to furnish the respective 3-substituted indoles (Entries **F**–**H**, Table 1). Furthermore, (*E*)-1-phenylnon-1-en-4-yn-3-yl acetate was also participated well in this reaction (Entries **K** and **L**, Table 1, Scheme 2).



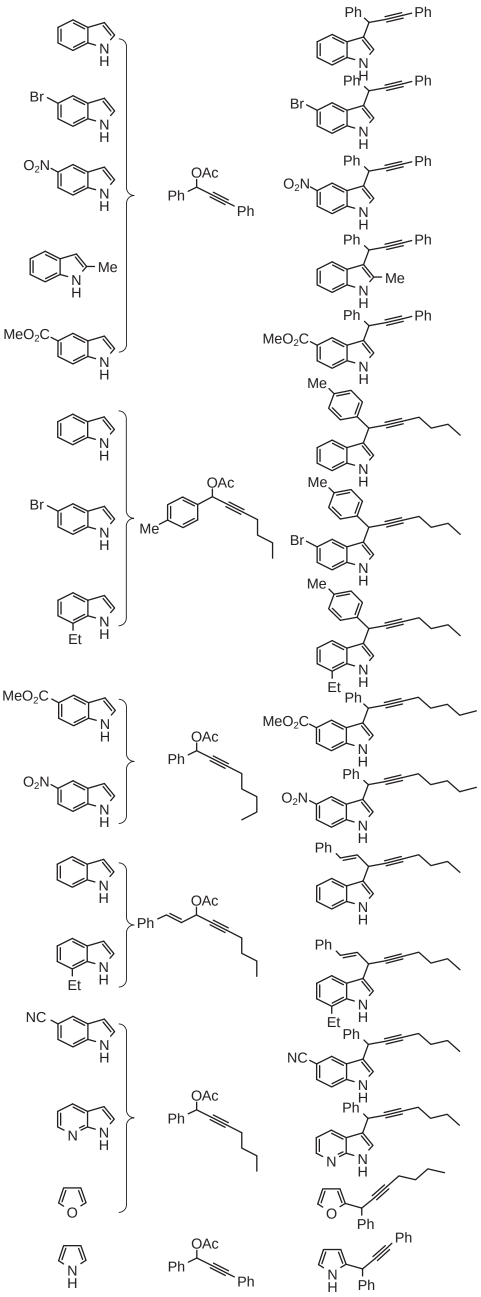
Scheme 1.



Scheme 2.

Like indole, pyrrole and furan gave the respective 2-propargylated pyrrole and furan derivatives (Entries **O** and **P**, Table 1). Interestingly, electron-deficient indoles such as 5-nitroindole, methyl 1*H*-indole-5-carboxylate and 5-cyanoindole also underwent smooth alkylation with propargylic acetates under similar reaction conditions to give the respective propargylated indoles (Entries **C**, **E**, **I**, **J**, and **M**, Table 1). In all cases, the reactions proceeded efficiently with high selectivity and completed within 25–50 min. However, in the absence of Amberlyst A-15®, no reaction was observed between indoles and propargylic acetates. No addition or rearranged products were observed in this reaction. The –OAc group was simply replaced by an indole in S_N2' manner. It is noteworthy to mention that a highly acid sensitive pyrrole and furan gave the desired propargylated derivatives without the formation of any side products arising from the polymerization. This is because of the sensitivity of pyrrole to strong acidic conditions. This method is compatible with ester, alkene, halide, nitro, and alkyne functionalities present in the molecule. The simple propargylic and homopropargylic acetates failed to undergo alkylation under similar reaction conditions. Furthermore, propargylic acetates derived from aliphatic aldehydes such as 1-cyclohexylhept-2-yn-1-ol did not undergo the expected S_N2' substitution with heteroaromatic systems. This method was successful only with propargylic acetates derived from aromatic and α,β-unsaturated aldehydes. As solvent, acetonitrile appeared to give the best results. All the products were characterized by ^{1}H, ^{13}C NMR, IR, and mass spectrometry. Among various solid acids such as montmorillonite KSF, phosphotungustic acid, and phosphomolybdic acid tested, Amberlyst-15® was found to give the best results in terms of conversion. The scope and generality of this process was illustrated with respect to various heteroaromatic systems and the results are presented in Table 1.[8] In summary, we have described an efficient alkylation of indoles with propargylic acetates using Amberlyst-15® as a novel promoter. In addition to its efficiency, simplicity, and mild reaction conditions, this method provides high yields of propargylated indoles in a short reaction time with high selectivity, which makes it a useful and attractive process for the alkylation of indoles. It is entirely a new synthetic route for the functionalization of indoles, pyrrole, and furan systems.

Table 1. Amberlyst-15® -catalyzed alkylation of heteroaromatic systems with propargylic acetates



Entry	Substrate	Propargylic acetates	Product[a]	Time/min	Yield/%[b]
A				30	91
B				35	93
C				50	85
D				35	88
E				35	87
F				30	90
G				40	92
H				35	87
I				50	86
J				35	84
K				30	91[c]
L				35	88[c]
M				35	92
N				30	89
O				45	86
P				50	84

[a]All products were characterized by ^{1}H, ^{13}C NMR, IR and mass spectroscopy. [b]Isolated and unoptimized yield. [c]E/Z ratio 9:1.

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8 General procedure. A mixture of indole (1.0 mmol), 1,3-diphenyl-2-propynyl acetate (1.0 mmol), and Amberlyst A-15® (0.5 g) in acetonitrile (5 mL) was stirred at 80 °C for the appropriate time (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, 2:8) to afford pure 3-propargylated indole. **3C**: **3-(1,3-diphenyl-2-propynyl)-5-nitro-1*H*-indole**: solid, mp 110–113 °C, IR (KBr): υ 3410, 2923, 2853, 1622, 1517, 1466, 1331, 1098, 755, 695 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.44 (s, 1H), 7.19–7.37 (m, 8H), 7.44–7.51 (m, 4H), 8.10 (dd, 1H, $J = 2.45$, 9.44 Hz), 8.31 (brs, 1H), 8.63 (d, 1H, $J = 1.7$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 31.8, 81.2, 87.2, 111.0, 111.6, 115.0, 122.7, 123.6, 125.4, 126.9, 128.3, 128.4, 128.5, 128.7, 129.0, 134.3, 140.4, 1421.8. LCMS: m/z: $(M + Na)^+$ 375. **3F**: **3-[1-(4-methylphenyl)-2-heptynyl]-1*H*-indole**: Liquid, IR (KBr): υ 3417, 3051, 2956, 2927, 2863, 1613, 1510, 1456, 1421, 1344, 1093, 772, 742 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (t, 3H, $J =$ 6.7 Hz), 1.36–1.57 (m, 4H), 2.24 (dt, 2H, $J = 2.2$, 6.7 Hz), 2.30 (s, 3H), 5.09 (s, 1H), 6.93–7.10 (m, 6H), 7.18–7.28 (m, 2H), 7.44 (d, 1H, $J = 8.3$ Hz), 7.81 (brs, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.4, 19.6, 22.3, 24.8, 32.2, 33.2, 75.4, 79.7, 111.9, 113.0, 118.9, 120.8, 121.6, 123.5, 127.4, 128.9, 129.0, 134.4, 135.5, 137.2. LCMS: m/z: $(M + Na)^+$ 324. **3P**: **2-(1,3-diphenyl-2-propynyl)-1*H*-pyrrole**: Solid, mp 69–72 °C, IR (KBr): υ 3429, 3058, 3028, 2925, 1706, 1597, 1490, 1448, 1292, 1073, 1027, 756, 719, 695 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.22 (s, 1H), 5.97 (m, 1H), 6.06 (dd, 1H, $J = 2.8$, 4.7 Hz), 6.60 (m, 1H), 7.18–7.33 (m, 6H), 7.37–7.46 (m, 4H), 8.02 (brs, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 34.2, 81.9, 88.6, 109.0, 110.2, 118.0, 123.4, 125.4, 127.4, 128.4, 128.6, 129.6, 130.5, 132.5, 140.1. LCMS: m/z: $(M + Na)^+$ 280.

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