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Indium(I) iodide as a radical initiator: intramolecular cyclization of functionalized bromo-alkynes to substituted tetrahydrofurans

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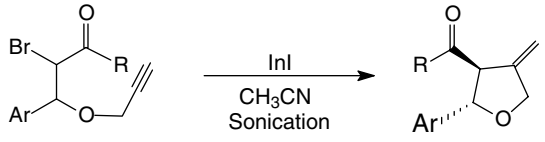
Abstract—Aryl substituted α-carbonyl bromo-alkynes undergo facile cyclizations to the corresponding substituted 4-methylene-tetrahydrofurans using indium(I) iodide in acetonitrile under sonication in high yields. The reaction is predicted to proceed via a radical process initiated by InI and a plausible radical pathway is suggested.

The concept and application of radicals has immensely enriched organic synthesis.[1] Although tributyltin hydride is used as a conventional radical reducing agent and has wide applications in radical cyclizations toward the construction of carbocyclic rings,[2] its toxicity and the difficulty of complete removal of tin species from reaction mixtures has posed serious problems. Therefore, substantial efforts have been made to find an alternative to tributyltin hydride.[3] Indium-mediated reactions have attracted considerable interest over the last decade because of the generally low toxicity of indium reagents and high efficiency in a variety of reactions.[4] Although indium metal has been demonstrated to participate in single electron transfer (SET) processes,[4] the use of indium in free radical cyclizations has not been explored to any great extent. Currently, efforts are ongoing in this direction and there has been a recent report of indium metal-mediated radical carbocyclizations,[5] although not very satisfactory with regard to general applicability and yields of the desired products (8–50%). Thus, a search for indium derivatives for effective radical cyclization is continuing. Recently In/I_2[6] and $InCl_3$–$NaBH_4$[7] have been used for atom-transfer and reductive radical cyclizations. As part of our activities on indium-mediated reactions[4e,8] and a current program to explore the novel utilities of indium(I) iodide[9] we report here an efficient InI-promoted reductive radical cyclization of appropriately substituted bromoalkynes to highly functionalized tetrahydrofurans (Scheme 1). Tetrahydrofuran derivatives are very useful precursors for the synthesis of a variety of antitumor agents and are constituents of a large number of sesquiterpenes and other natural products.[10]

Several structurally varied aryl substituted α-carbonyl bromoalkynes underwent cyclization in the presence of indium(I) iodide under sonication to give the corresponding substituted 4-methylene tetrahydrofurans using this procedure.[11] The results are summarized in Table 1. The products were obtained in high purity by column chromatography over silica gel. The stereochemistry of the substituents was established by comparison of their ^1H NMR and ^{13}C NMR spectroscopic data with those reported for known compounds.[12]

The reactions are, in general clean, although 5–10% of reduced product was formed, which was separated easily during purification. Without sonication the reaction did not proceed at all at room temperature with stirring. Heating at reflux led to the formation of other unidentified side products. The optimum amount of InI for an



Scheme 1.

Keywords: Indium(I) iodide; Radical; Bromo-alkyne; Tetrahydrofuran; Ultrasound.
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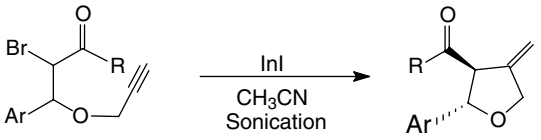
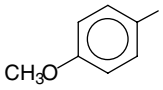
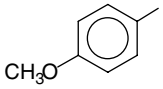
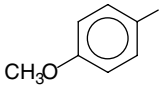
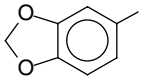
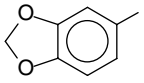
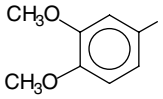
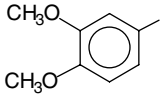
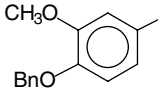
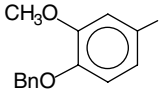
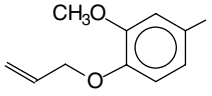
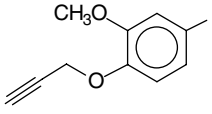
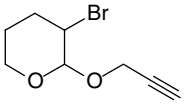
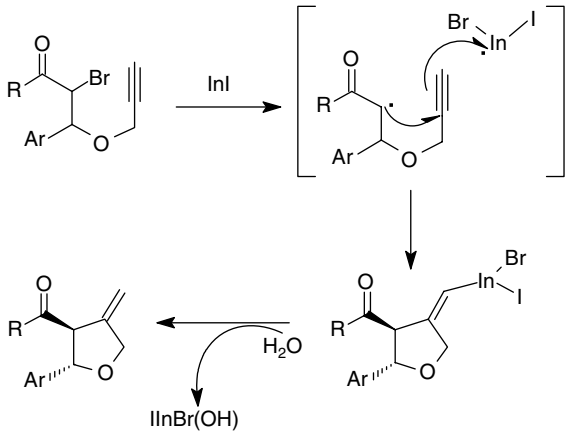
Table 1. Synthesis of substituted tetrahydrofurans by radical cyclization promoted by InI



Entry	Ar	R	Time (h)	Yield[a] (%)
1		CH_3	3.0	68
2		OCH_2CH_3	3.5	75
3		OCH_3	3.0	65
4		CH_3	3.0	62
5		OCH_2CH_3	3.5	70
6		OCH_2CH_3	4.0	69
7		CH_3	3.5	65
8		OCH_2CH_3	3.5	80
9		CH_3	4.0	60
10		OCH_2CH_3	3.0	70
11		OCH_2CH_3	3.5	68
12		No reaction		

[a] Yields refer to those of pure isolated products characterized by IR and ^1H and ^{13}C NMR spectroscopic data.

efficient reaction was found to be 1 equiv. The reaction did not proceed at all in less polar solvents such as methylene chloride; acetonitrile was found to be the best choice. The starting bromoalkynes were prepared from the corresponding cinnamyl esters by reaction with *N*-bromosuccinimide in the presence of the appropriate alcohol following standard procedures.[10,13]



Scheme 2.

It was observed that the presence of a radical quencher such as *p*-benzoquinone and TEMPO (2,2,6,6-tetramethylpiperidine oxide) in the reaction mixture completely arrested the cyclization process. This indicates that the reaction possibly proceeds via a radical path. It was also found that an aryl substituent with an electron donating group and an α-bromocarbonyl moiety were two essential requirements for an effective reaction (a bromoalkyne without these functionalities (entry 12) did not undergo any cyclization). Possibly, the radical formed after abstraction of Br is stabilized by the adjacent carbonyl functionality, and without such stabilization (entry 12) the reaction did not proceed. This evidence favors radical cyclization and thus a radical pathway is predicted as outlined in Scheme 2.

In conclusion, the present procedure using indium(I) iodide as a selective radical initiator provides an efficient and simple method for the synthesis of highly functionalized tetrahydrofurans, which are synthetically very important molecules. The notable features of this method are fast reactions times (3–4 h), good isolated yields of products (60–80%), simple purification procedure, and apparent non-toxicity of InI. Most significantly, the potential of indium(I) iodide as a radical initiator is demonstrated and to the best of our knowledge this work reports the first use of InI for this type of radical cyclization. This observation provides great promise toward more useful applications of InI in organic synthesis.

Acknowledgments

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11. *Representative experimental procedure for the synthesis of 2-(4-methoxyphenyl)-4-methylene-tetrahydrofuran-3-carboxylic acid ethyl ester (entry 2).* 2-Bromo-3-(4-methoxyphenyl)-(3-prop-2-ynyloxy)propionic acid ethyl ester (341 mg, 1 mmol) in dry acetonitrile (8 mL) was sonicated in an ultrasonic bath (bath temperature: 40–45 °C) in the presence of indium(I) iodide (242 mg, 1 mmol) for 3.5 h (TLC). The reaction mixture was quenched with a few drops of H_2O. Acetonitrile was evaporated and the residue was then extracted with ether (3×20 mL). The organic extract was washed with brine, dried (Na_2SO_4), and evaporated to leave the crude product, which was purified by column chromatography over silica gel (hexane/ether 4:1) to give pure 2-(4-methoxyphenyl)-4-methylene-tetrahydrofuran-3-carboxylic acid ethyl ester (197 mg, 75%) as a colorless liquid. IR (neat) 1514, 1604, 1732 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.26 (t, $J = 2.88$ Hz, 3H), 3.79 (s, 3H), 4.12–4.26 (m, 2H), 4.45–4.64 (m, 3H), 5.08–5.19 (m, 3H), 6.87 (d, $J = 8.79$ Hz, 2H), 7.30 (d, $J = 8.79$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.2, 55.3, 57.0, 61.1, 71.5, 83.2, 106.2, 113.9 (2C), 127.5 (2C), 129.7, 146.6, 159.5, 170.7. Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.54; H, 6.91. This procedure was followed for reactions of all the substrates listed in Table 1. The products (entries 1, 3, and 5–8), which are known[12] were identified by comparison of their spectroscopic data (IR, ^1H NMR, and ^{13}C NMR) with those reported. New compounds (entries 2, 4, and 9–11) were characterized from their spectroscopic data and elemental analysis. These data are presented below:
1-(2-Benzo[1,3]dioxol-5-yl)-4-methylene-tetrahydrofuran-3-yl-ethanone (entry 4). Colorless liquid; IR (neat): 1504, 1605, 1713 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.24 (s, 3H), 3.61–3.64 (m, 1H), 4.44–4.61 (m, 2H), 5.08–5.18 (m, 3H), 5.95 (s, 2H), 6.77–6.83 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.0, 65.3, 71.4, 82.8, 100.9, 106.2, 107.1, 108.0, 119.4, 134.2, 146.5, 147.3, 147.8, 205.1. Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.34; H, 5.62.
1-[2-(4-Benzyloxy-3-methoxy-phenyl)-4-methylene-tetrahydrofuran-3-yl] ethanone (entry 9). Yellowish gummy liquid; IR (neat): 1514, 1593, 1711 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 22.4 (s, 3H), 3.65–3.68 (m, 1H), 3.88 (s, 3H), 4.45–4.50 (m, 2H), 5.07–5.21 (m, 5H), 6.78–6.90 (m, 3H), 7.26–7.44 (m, 5H);^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.1, 55.9, 65.1, 70.8, 71.4, 82.8, 107.0, 109.4, 113.7, 118.1, 127.1 (2C), 127.7, 128.4 (2C), 133.2, 136.9, 146.7, 147.8, 149.7, 205.3. Anal. Calcd for $C_{21}H_{22}O_4$: C, 74.54; H, 6.55. Found: C, 74.36; H, 6.47.
2-(4-Allyloxy-3-methoxy-phenyl)-4-methylene-tetrahydrofuran-3-carboxylic acid ethyl ester (entry 10). Colorless liquid; IR (neat): 1512, 1596, 1632, 1732 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.28 (t, $J = 7.20$ Hz, 3H), 3.46–3.50 (m, 1H), 3.88 (s, 3H), 4.17–4.27 (m, 2H), 4.47–4.66 (m, 4H), 5.10–5.20 (m, 3H), 5.29–5.42 (m, 2H), 5.99–6.17 (m, 1H), 6.82–7.08 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1, 55.7, 56.9, 61.0, 69.7, 71.3, 83.2, 106.1, 109.3, 113.0, 117.8, 118.2, 122.2, 132.5, 133.1, 144.3, 146.4, 170.6. Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 67.82; H, 6.86.
2-(3-Methoxy-4-prop-2-ynyloxy-phenyl)-4-methylene-tetrahydrofuran-3-carboxylic acid ethyl ester (entry 11). Colorless liquid; IR (neat): 1512, 1589, 1728, 2070 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.28 (t, $J = 7.2$ Hz, 3H), 2.51 (t, $J = 2.4$ Hz, 1H), 3.46–3.50 (m, 1H), 3.87 (s, 3H), 4.18–4.29 (m, 2H), 4.46–4.66 (m, 2H), 4.75 (d, $J = 2.4$ Hz, 2H), 5.09–5.20 (m, 3H), 6.89–7.03 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1, 55.7, 56.8, 56.9, 61.0, 71.3, 75.6, 78.4, 83.1, 106.2, 109.4, 114.0, 118.2, 133.7, 146.3 (2C), 149.6, 170.5. Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.16; H, 6.32.
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