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$InBr_3$-catalyzed annulations of cyclic 1,3-diketones with aryl propargyl alcohols: a novel synthesis of 2,4-diaryldihydropyrans

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ABSTRACT

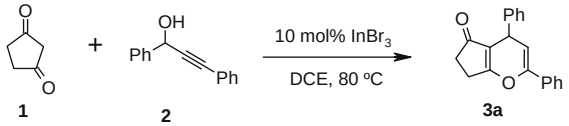
The cyclic 1,3-dicarbonyl compounds undergo smooth cyclization with aryl propargyl alcohols in the presence of 10 mol % indium tribromide in refluxing dichloroethane to produce 2,4-diarylpyran derivatives in good yields with high selectivity.

Lewis acid catalyzed carbon–carbon bond-forming reactions are of great significance in organic synthesis because of their high reactivity, selectivity, and mild reaction conditions.[1] Aryl propargyl methanols 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.[2,3] The direct nucleophilic substitution of the hydroxy group in alcohols with nucleophiles generally requires preactivation of the alcohol because of its poor leaving ability.[4] Consequently, hydroxyl groups are transformed into the corresponding halides, carboxylates, carbonates, phosphonates, or related compounds.[5] Recently, acid catalysts such as $BF_3{\cdot}OEt_2$, $InCl_3$, $Bi(OTf)_3$, $Yb(OTf)_3$, $FeCl_3$, and *H*-montmorillonite have been employed to perform nucleophilic substitution of benzylic alcohols with active methylene compounds.[6,7] In most cases, either a high reaction temperature or a promoter is required to enhance the leaving ability of the hydroxyl group. However, only few methods have been reported for the direct substitution of propargylic alcohols with 1,3-dicarbonyls.[8] The coupling of 1,3-diketones with α,β-unsaturated ketones has been reported for the synthesis of 5-oxo-tetrahydro-4*H*-benzo-[*b*]-pyrans.[9] Recently, the coupling of cyclopentanediones with propargyl alcohols has been achieved using Ru/TFA catalyst system.[10] Therefore, the development of simple, convenient, and one-pot approaches for direct catalytic substitution of alcohols with cyclic 1,3-dicarbonyls would extend its use in the synthesis of biologically interesting heterocycles.

Recently, indium tribromide has received increasing attention as a water-tolerant Lewis acid catalyst for organic synthesis demonstrating highly chemo-, regio-, and stereo-selective results.[11] Compared to conventional Lewis acids, it has advantages of water stability, recyclability, operational simplicity, strong tolerance to oxygen, and nitrogen-containing substrates and functional groups, and it can often be used in catalytic amounts.[12]

Following our interest in catalytic uses of indium tribromide,[13,14] we herein, report for the first time, an efficient alkylation of cyclic 1,3-dicarbonyl compounds with propargylic alcohols using a catalytic amount of $InBr_3$. Accordingly, we first attempted the alkylation of cyclopentane-1,3-dione (**1**) with 1,3-diphenyl-2-propyn-1-ol (**2**) in 1,2-dichloroethane in the presence of 10 mol % of $InBr_3$. The reaction went to completion in 2.0 h and the desired product, 2,4-diphenyl-6,7-dihydrocyclopenta-[*b*]pyran-5(4*H*)-one, **3a** was obtained in 85% yield (Scheme 1).

Encouraged by this result, we turned our attention to various cyclic 1,3-diketones and aryl propargyl alcohols. Interestingly, cyclic 1,3-diketones such as cyclohexane-1,3-dione and 5,5-dimethyl-1,3-cyclohexanedione (dimedone) reacted well with 1,3-diphenyl-2-propyn-1-ol to give the corresponding 2,4-diphenyl-7,8-dihydro-4*H*-chromen-5(6*H*)-one derivatives in good yields (Table 1, entries **b** and **c**). Various aryl propargyl alcohols such as



Scheme 1.

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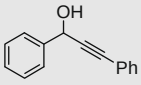
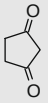
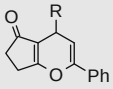
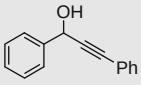
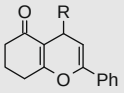
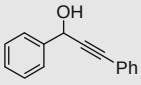
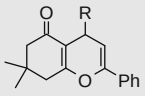
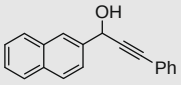
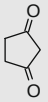
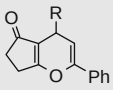
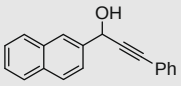
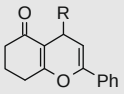
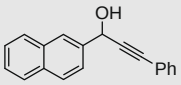
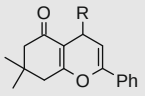
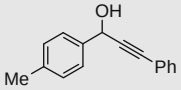
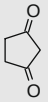
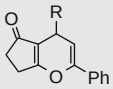
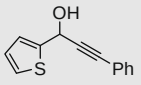
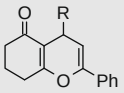
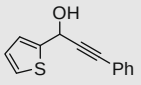
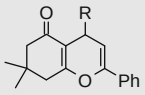
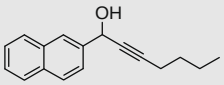
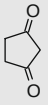
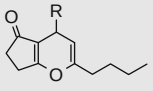
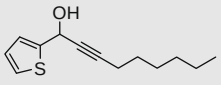
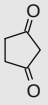
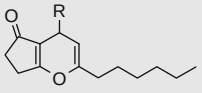
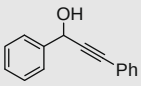
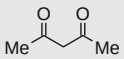
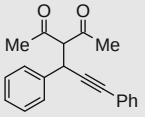
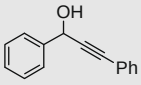
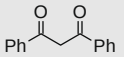
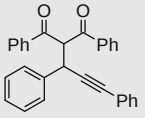
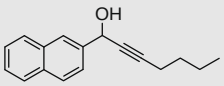
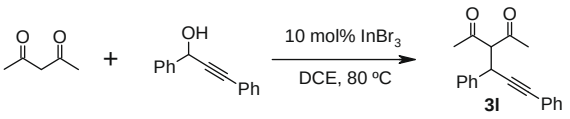
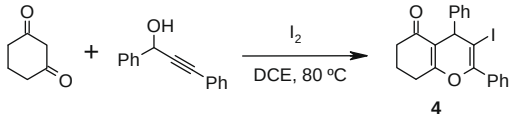
Table 1
Indium tribromide-catalyzed synthesis of 2,4-disubstituted pyrans

Entry	Propargyl alcohol	1,3-Diketone	Product[a]		Time (h)	Yield[b] (%)
a				R = phenyl	2.0	85
b				R = phenyl	2.0	83
c				R = phenyl	1.5	80
d				R = 2-naphthyl	2.5	89
e				R = 2-naphthyl	2.0	86
f				R = 2-naphthyl	2.0	88
g				R = tolyl	2.5	90
h				R = 2-thienyl	2.0	87
i				R = 2-thienyl	1.5	85
j				R = 2-naphthyl	1.0	82
k				R = 2-thienyl	1.5	86
l					1.0	85
m					5.0	89
n				R = *n*-butyl	1.0	90
o				R = *n*-butyl	1.5	88

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



Scheme 2.



Scheme 3.

1-(naphthalen-2-yl)-3-phenylprop-2-yn-1-ol, 1-(naphthalen-2-yl)hept-2-yn-1-ol, 3-phenyl-1-*p*-tolylprop-2-yn-1-ol, 3-phenyl-1-(thiophen-2-yl)prop-2-yn-1-ol, and 1-(thiophen-2-yl)hept-2-yn-1-ol reacted effectively with cyclic 1,3-diketones to furnish the respective dihydropyran derivatives (Table 1, entries **d**–**k**). In case of acyclic 1,3-diketones such as acetyl acetone and 1,3-diphenylpropane-1,3-dione, no cyclized products were obtained under identical conditions (Scheme 2, Table 1, entries **l**–**o**).

Next, we attempted alkylation of cyclohexane-1,3-diketone with 1,3-diphenyl-2-propyn-1-ol using molecular iodine as a catalyst. The reaction proceeded smoothly in the presence of equimolar amount of iodine in refluxing 1,2-dichloroethane. The reaction went to completion in 3 h and the product, 3-iodo-2,4-diphenyl-7,8-dihydro-4*H*-chromen-5(6*H*)-one, **4** was obtained in 75% yield (Scheme 3).

However, in the absence of iodine or indium tribromide, the above reactions (Schemes 1–3) did not proceed even after 12 h. No addition or rearranged products were observed in this reaction. The hydroxyl group was simply replaced by 1,3-diketone. Furthermore, propargylic alcohols derived from aliphatic aldehydes such as 1-cyclohexylhept-2-yn-1-ol did not undergo the expected cyclization. This method was successful only with propargylic alcohols derived from aromatic aldehydes. As solvent, dichloroethane appeared to give the best results. The products were characterized by ^{1}H, ^{13}C NMR, IR, and mass spectroscopy. Among various metal halides such as $InCl_3$, $CeCl_3{\cdot}7H_2O$, $SmCl_3$, and $YbCl_3$, indium tribromide was found to give the best results. The scope and generality of this process were illustrated with respect to various 1,3-diketones and aryl propargyl alcohols and the results are presented in Table 1.[15]

In summary, we have developed a novel method for the preparation of dihydropyrans from cyclic 1,3-diketones and aryl propargyl alcohols using catalytic amount of indium tribromide as catalyst. In addition to its simplicity and efficiency, this method provides high yields of products with high selectivity, which makes it a useful and attractive process for the preparation of dihydropyran derivatives in a single step operation.

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15. *Experimental procedure*: A mixture of 1,3-dicarbonyl compound (2.0 mmol), alcohol (1.0 mmol), and $InBr_3$ (10 mol %) in dichloroethane (5 mL) was refluxed to 80 °C for appropriate time. After completion of the reaction as indicated by TLC, the reaction mixture was filtered and diluted with water and extracted with dichloromethane (2 × 15 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, 1:9) to afford pure products as shown in Table 1. The spectroscopic data of the products were identical with the data reported in the literature. Spectral data for selected products:
Compound **3a**: *2,4-diphenyl-4,5,6,7-tetrahydrocyclopenta[b]pyran-5-one*: Pale yellow color solid, mp 166–168 °C; IR (KBr): ν_{max} 2923, 2852, 2254, 2127, 1698, 1668, 1627, 1386, 1230, 1026, 1001, 826, 761, 694 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.41–2.46 (m, 2H), 2.75–2.82 (m, 2H), 4.40 (d, 1H, J = 4.4 Hz), 5.64 (d, 1H, J = 4.4 Hz), 7.15–7.41 (m. 8H), 7.58–7.62 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.5, 33.4, 35.5, 103.9, 117.0, 124.6, 126.9, 128.1, 128.4, 129.0, 130.9, 132.7, 143.0, 148.3, 178.4, 202.7; EIMS (M+Na): *m/z*: 311.
Compound **3d**: *4-(2-naphthyl)-2-phenyl-4,5,6,7-tetrahydro-cyclopenta[b]pyran-5-one*: Colorless solid, mp 181–184 °C; IR (KBr): ν_{max} 2923, 2854, 1670, 1626, 1387, 1232, 1129, 1004, 817, 759, 695, 594, 477 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.47–2.51 (m, 2H), 2.82–2.87 (m, 2H), 4.63 (d, 1H, J = 3.7 Hz), 5.75 (d, 1H, J = 4.5 Hz), 7.37–7.51 (m, 6H), 7.65–7.82 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.5, 33.3, 35.7, 103.7, 116.9, 124.6, 125.5, 125.9, 126.4, 126.6, 127.5, 127.7, 128.2, 128.4, 129.0, 132.5, 132.6, 133.3, 140.4, 148.4, 178.5, 202.6; EIMS (M+Na): *m/z*: 361.
Compound **3g**: *4-(4-methylphenyl)-2-phenyl-4,5,6,7-tetrahydro- cyclopenta[b]-pyran-5-one*: Colorless solid, mp 180–182 °C; IR (KBr): ν_{max} 2922, 2852, 1703, 1674, 1628, 1386, 1231, 1002, 816, 763, 696, 513 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.31 (S, 3H), 2.42–2.46 (m, 2H), 2.74–2.79 (m, 2H), 4.38 (d, 1H, J = 4.1 Hz), 5.62 (d, 1H, J = 4.1 Hz), 7.06–7.09 (d, 2H, J = 7.9 Hz), 7.15–7.18 (d, 2H, J = 8.1 Hz), 7.31–7.39 (m, 3H), 7.57–7.61 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0, 25.6, 33.3, 35.2, 104.0, 117.2, 124.7, 127.9, 128.4, 128.9, 129.2, 132.7, 136.5, 140.1, 148.2, 178.3, 202.7; EIMS (M+Na): *m/z*: 325.
Compound **3h**: *2-phenyl-4-(2-thienyl)-5,6,7,8-tetrahydro-4H-5-chromenone*: Brown liquid, IR (Neat): ν_{max} 3065, 2923, 2853, 1662, 1625, 1379, 1213, 1185, 1022, 764, 694, 555, 522 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.01–2.10 (m, 2H), 2.30–2.49 (m, 2H), 2.55–2.74 (m, 2H), 4.82 (d, 1H, J = 5.2 Hz), 5.78 (d, 1H, J = 5.2 Hz), 6.85–6.87 (m, 1H), 6.92 (d, 1H, J = 3.0 Hz), 7.07–7.09 (dd, 1H, J = 5.2, 1.5 Hz), 7.29–7.38 (m, 3H), 7.56–7.59 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.3, 27.6, 29.7, 37.0, 103.5, 113.7, 124.1, 124.4, 124.6, 126.7, 128.4, 128.9, 132.8, 147.5, 149.6, 166.1, 197.2; EIMS (M+Na): *m/z*: 331.
Compound **3m**: *2-(1,3-diphenyl-2-propynyl)-1,3-diphenyl-1,3-propanedione*: Colorless, solid, mp 91–92 °C; IR (KBr): ν_{max} 3062, 2923, 2853, 1686, 1658, 1591, 1490, 1446, 1285, 1253, 1196, 988, 755, 687, 561, 523 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.14 (d, 1H, J = 9.8 Hz), 5.76 (d, 1H, J = 10.5 Hz), 6.98–7.02 (m, 2H), 7.09–7.30 (m, 8H), 7.39–7.58 (m, 6H), 7.72–7.76 (m, 2H), 8.08–8.11 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 38.7, 62.9, 85.0, 89.3, 122.8, 127.3, 127.8, 128.3, 128.5, 128.8, 129.0, 131.3, 133.3, 133.4, 136.3, 136.8, 139.1, 192.4; EIMS (M+Na): *m/z*: 437.