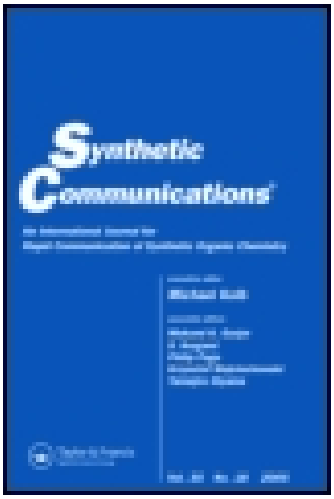

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Sandip K. Nayak [a], Suchitra Bhatt [a] & Kshama Roy [a]

[a] Bio-organic Division, Bhabha Atomic Research Centre, Mumbai, India

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INTRAMOLECULAR KETONE-OLEFIN RADICAL CYCLIZATION WITH LOW-VALENT TITANIUM REAGENT: SYNTHESIS OF BENZOPYRANS

Sandip K. Nayak, Suchitra Bhatt, and Kshama Roy
Bio-organic Division, Bhabha Atomic Research Centre, Mumbai, India

A novel protocol for intramolecular ketyl-olefin radical cyclization with low-valent titanium reagent is outlined. It allows the formation of the benzopyran nucleus from* ortho-*allyloxy propiophenones as the sole product in moderate yields via intramolecular radical cyclization.

Keywords: Benzopyran; intramolecular radical cyclization; low-valent titanium reagent; *ortho*-allyloxy aromatic aldehydes/ketones

INTRODUCTION

Carbon–carbon bond-formation reactions are of great importance and continue to draw attention to synthetic organic chemists. Intramolecular cyclization of the carbon radical to multiple bonds has been extensively used as a useful tool in organic synthesis.[1] Among those, intramolecular ketyl-olefin cyclization has many advantages, especially in terms of high diastereoselectivities at newly formed C−C bond in the cyclized product. Samarium(II) iodide[2] and organotin reagents[3] have been commonly exploited for ketyl-olefin radical cyclization reactions relative to other low-valent metals. Although Ti(0)[4] has been routinely used for the synthesis of 1,2-diol/olefins from aldehydes/ketones, there is no report on its application in carbonyl-olefin/alkyne radical cyclization reactions. Herein, we report an unprecedented Ti(0) reagent–mediated intramolecular ketyl-olefin radical cyclization in 2-allyloxy aromatic ketones leading to the formation of the benzopyran skeleton, which is an important motif of many biologically active oxygen heterocycles (Scheme 1).

RESULTS AND DISCUSSION

The reductive deoxygenation of carbonyl compounds to olefins with low-valent titanium (LVT) reagents has found wide range of applications, from the synthesis of strained olefins to the synthesis of various complex natural products including taxol.[4,5] The reaction proceeds by single-electron transfer (SET) from LVT to the substrate to form a radical anion (ketyl), which undergoes fast dimerization to the

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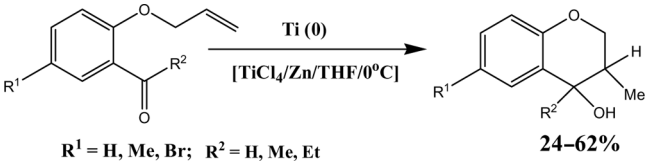
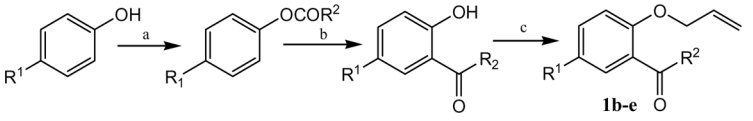
Address correspondence to Sandip K. Nayak, Bio-organic Division, Bhabha Atomic Research Centre, Mumbai 400085, India. E-mail: sknayak@barc.gov.in



Scheme 1. Low-valent titanium (LVT)–mediated intramolecular carbonyl-olefin radical cyclization in *ortho*-allyloxy aromatic aldehydes/ketones.

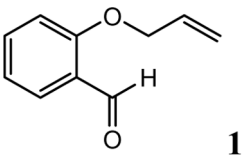
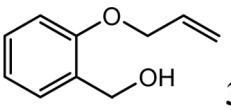
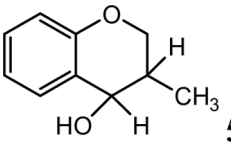
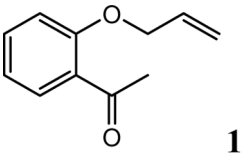
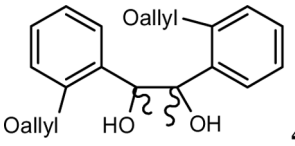
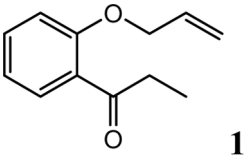
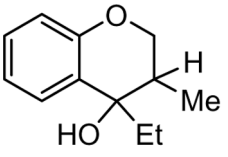
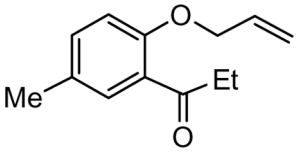
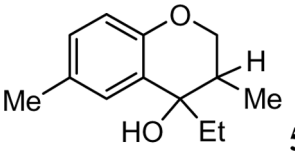
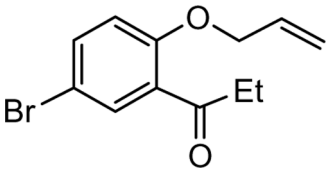
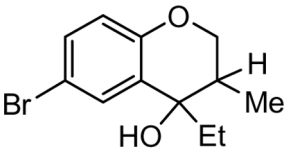
titanium pinacolate. The pinacolates are usually stable at 0 °C, whereas at higher temperatures they undergo deoxygenation to liberate olefin. The titanium oxides formed in the reaction serve as the thermodynamic sink that drives the conversion. So far, the McMurry reaction had been essentially confined to inter- and intramolecular coupling (i) between two aldehydes/ketones and (ii) ketoesters/ketoamides, respectively. Although intramolecular carbonyl-olefin radical cyclization with SmI_2 has been amply demonstrated by Molander et al.,[2] to the best of our knowledge there is no report on the use of Ti(0) reagent in intramolecular carbonyl-olefin radical cyclization reactions. The only report so far by Roy et al. for this cyclization is based on the titanium(III) (Cp_2TiCl) reagent.[6]

In continuation of our work on the synthetic applications of LVT reagents,[7] we envisaged that the initially formed ketyl radical of *ortho*-alkenyloxy aromatic aldehyde/ketone (**2**) may undergo intramolecular C–C bond formation to the sterically close olefin moiety in the *ortho* position to afford a carbocyclic skeleton **5** before its dimerization to the 1,2-diol **4** or abstraction of H from solvent to form **3** (Scheme 3). To this end, a preliminary study on carbonyl-olefin coupling reaction was carried out with *ortho*-allyloxybenzaldehyde (**1a**) as a substrate. Thus, reaction of **1a** with LVT reagent [Ti(0) prepared from $TiCl_4$/Zn/tetrahydrofuran (THF)] at 0 °C yielded a mixture of two products, which were characterized as 2-allyloxy benzyl alcohol (**3a**) (possibly by the abstraction of hydrogen from THF by the initially formed ketyl radical; path A) and 4-hydroxy-3-methyl-benzopyran (**5a**) (by intramolecular radical cyclization; path C) (Table 1, entry 1) by infrared (IR), ^{1}H NMR, and ^{13}C NMR data. The structure of compound **5a** was further confirmed by its oxidation to 3-methyl-benzopyran-4-one[8] (**6**) by pyridinium chlorochromate (PCC). However, under identical reaction conditions, *ortho*-allyloxyacetophenone (**1b**), instead of intramolecular radical cyclization to chromanol **5b**, underwent reductive dimerization to afford the corresponding 1,2-diol (**4b**) (path B) as the sole product in moderate yield (Table 1, entry 2). This prompted us to study the role of different carbonyl functions *ortho*- to allyloxy group in carbonyl-olefin radical cyclization. Gratifyingly, the reaction of *ortho*-allyloxypropiophenone (**1c**) with the LVT reagent under identical reaction conditions led to intramolecular radical cyclization only (path C), affording 4-ethyl-4-hydroxy-3-methyl-benzopyran (**5c**) as the sole



Scheme 2. Synthesis of 5′-substituted-2′-allyloxypropiophenones from 4-substituted phenols.

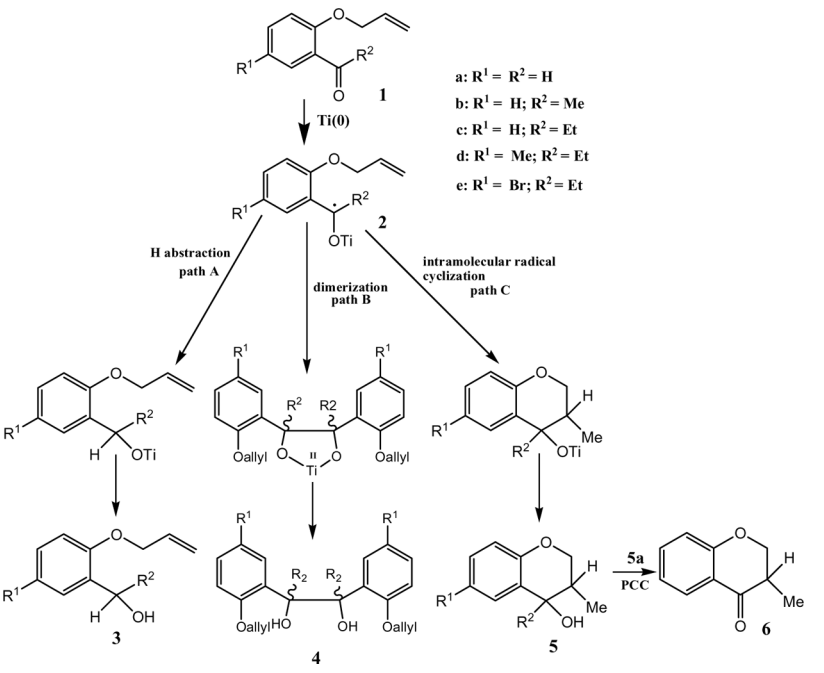
Table 1. Reactions of *ortho*-allyloxy aromatic aldehydes/ketones with low-valent titanium reagent ($TiCl_4$/Zn/THF) at 0 °C

Entry	Substrate	Time (h)	Product	Yield (%)[a]
1	 **1a**	3.0	 **3a**	56.0
			 **5a**	24.0
2	 **1b**	3.0	 **4b**	60
3	 **1c**	3.0	 **5c**	62.0
4	 **1d**	12.0	 **5d**	56.0
5		12.0	 **5e**	45.0

[a]Isolated yield after column chromatography.

product in moderate yield without any side product (Table 1, entry 3). More strikingly, ^{1}H NMR and ^{13}C NMR data revealed the formation of only one of the two possible diastereomers of **5c**. However, we could not unequivocally establish the relative stereochemistry at C-3 and C-4 of **5c** from nuclear Overhauser effect (NOE) spectral data.

To see the generality and scope of the reaction, two more 5′-substituted 2′-allyloxy propiophenones (**1d** and **1e**) were prepared from 4-substituted phenols in three steps: (i) esterification of phenols to corresponding arylalkanoates, (ii)



Scheme 3. Fate of LVT-generated ketyl radical in *ortho*-allyloxy aromatic aldehydes/ketones. (a) R^2COCl, NEt_3, dichloromethane, rt; (b) $AlCl_3$, 130 °C; and (c) K_2CO_3, allylbromide, acetone, reflux.

$AlCl_3$-catalyzed Fries migration to 2-acyl-4-substituted phenols, and (iii) allylation of phenols with K_2CO_3/allylbromide (Scheme 2), and then subjected to the LVT reagent at low temperature. In both the cases, corresponding 4-chromanols **5d** and **5e** were obtained in moderate yields (Table 1, entries 4 and 5). The results are summarized in Table 1. As in the case of **5c**, only one of the two possible diastereomers of both **5d** and **5e** were formed. Although IR, ^1H NMR, and ^{13}C NMR data of the compounds **5c–e** corroborated their structures, attempts to record their mass spectra remained unsuccessful for unknown reasons.

CONCLUSION

In conclusion, hitherto unknown LVT reagent [Ti(0)]–mediated intramolecular carbonyl-olefin radical cyclization of *ortho*-allyloxy propiophenones has been developed. This has led to the synthesis of benzopyran derivatives, which constitute an important class of biologically active oxygen heterocycles. More important, only one of the two possible benzopyran diastereomers was formed during the radical cyclization. The mechanistic investigation is under way.

EXPERIMENTAL

IR spectra were scanned with a Jasco Fourier transform (FT)–IR 4100 spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded with a Bruker AC 200

spectrometer with tetramethylsilane (TMS) as internal standard. Microanalysis was performed with a Carlo Erba elemental analyzer (model 1110). $TiCl_4$ was purchased from Aldrich Chemical Co. USA and used without further purification. THF was freshly distilled over sodium-benzophenone. All reactions were carried out under an argon atmosphere.

Typical Procedure for Intramolecular Carbonyl-Olefin Radical Cyclization of *o*-Allyloxy Propiophenone (1c) to 4-Ethyl-3-methyl-2H-benzopyran-4-ol (5c) with Low-Valent Titanium Reagent

$TiCl_4$ (3.0 ml, 27.0 mmol) was added slowly to a well-stirred ice-cooled suspension of zinc dust (3.5 g, 54.0 mmol) in dry THF (80 ml), and then the mixture was allowed to attain room temperature before refluxing for 3 h. The black mixture was then brought to room temperature and cooled in an ice-water bath. A solution of **1c** (1.7 g, 9.0 mmol) in THF (5 ml) was added dropwise to the black suspension of LVT reagent and stirred further at 0 °C. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, the mixture was diluted with ethyl acetate, quenched with 10% aqueous K_2CO_3 solution (10 ml), and stirred for 2 h. The mixture was passed through a bed of celite, and the filtrate was washed with brine and dried (Na_2SO_4). Removal of solvent followed by column chromatography (SiO_2) yielded **5c** (1.07 g, 62% yield).

Spectral Data of Some Selected Compounds

2-Allyloxybenzylalcohol (3a). Oil; IR (neat): $\nu = 3449$, 2926, 2361, 1600, 1491, 1454, 1238, 1023, 912 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.44 (br s, 1H, OH), 4.51 (d, 2H, $J = 5.0$ Hz), 4.71 (s, 2H), 5.35 (m, 2H), 6.04 (m, 1H), 6.83 (d, 1H, $J = 8.2$ Hz), 6.96 (t, 1H, $J = 7.2$ Hz), 7.24 (m, 1H), 7.35 (d, 1H, $J = 7.2$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 60.5, 68.2, 110.9, 116.8, 120.4, 127.9, 128.0, 129.2, 132.8, 155.6.

3-Methyl-benzopyran-4-ol (5a). Oil; IR (neat): $\nu = 3399$, 2968, 2878, 2357, 1610, 1584, 1488, 1042, 1019 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.01 (dd, 3H, $J = 7.0$, 14.0 Hz), 2.02 (m, 1H), 2.89 (br s, 1H, OH), 3.89 (m, 1H), 4.21 (m, 1H), 4.56 (m, 1H), 6.87 (m, 2H), 7.24 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 11.5, 13.6, 32.5, 34.5, 66.3, 66.4, 67.5, 69.3, 116.3, 116.5, 120.2, 120.5, 123.7, 124.2, 129.1, 129.4, 130.1, 153.9. Anal. calcd. for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 72.97; H, 7.18.

2,3-Dihyro-3-methylchromen-4-one (6)[8]. Oil; IR (neat): $\nu = 3060$, 3031, 2981, 2940, 2921, 2879, 1647, 1618, 1182, 1090, 1014, 969 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.17 (d, 3H, $J = 8.0$ Hz), 2.81 (m, 1H), 4.09 (t, 1H, $J = 11.0$ Hz), 4.45 (dd, 1H, $J = 5.0$, 11.2 Hz), 6.94 (m, 2H), 7.41 (m, 1H), 7.85 (dd, 1H, $J = 2.0$, 8.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 10.5, 40.5, 72.0, 117.6, 120.4, 121.1, 127.1, 135.5, 135.7, 161.6, 194.6.

2,3-Bis-(2-(allyloxy)phenyl)butan-2,3-diol (4b). Oil; IR (neat): $\nu = 3497$, 3079, 3009, 2985, 2941, 2878, 1599, 1579, 1489, 1228, 1120, 1056 cm^{-1}; ^1H NMR

(200 MHz, $CDCl_3$): δ 1.64 (s, 6H), 4.20 (ddd, 4H, $J = 5.3$, 12.5, 17.8 Hz), 5.28 (m, 4H), 5.55 (br s, 2H, OH), 5.87 (m, 2H), 6.76 (m, 4H), 6.99 (d, 2H, $J = 7.4$ Hz), 7.12 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.6, 69.4, 82.3, 112.6, 118.0, 120.3, 128.0, 129.9, 132.1, 132.7, 156.9. Anal. calcd. for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.35; H, 7.21.

4-Ethyl-3-methyl-benzopyran-4-ol (5c). Oil; IR (neat): $\nu = 3456$, 2969, 2938, 2880, 1608, 1581, 1044 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.74 (t, 3H, $J = 7.5$ Hz), 1.00 (d, 3H, $J = 7.0$ Hz), 1.75 (brs, 1H, OH), 2.09 (m, 3H), 3.94 (m, 1H), 4.08 (dd, 1H, $J = 3.7$, 10.9 Hz), 6.81 (d, 1H, $J = 8.1$ Hz), 6.92 (m, 1H), 7.17 (m, 1H), 7.41 (dd, 1H, $J = 1.5$, 7.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 8.6, 9.9, 31.1, 33.2, 67.8, 71.2, 116.9, 120.6, 126.1, 126.7, 128.9, 154.6. Anal. calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.80; H, 8.23.

4-Ethyl-3,6-dimethyl-benzopyran-4-ol (5d). Oil; IR (neat): $\nu = 3454$, 2969, 2938, 2880, 1498, 1136, 1036 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.75 (t, 3H, $J = 7.5$ Hz), 1.01 (d, 3H, 6.9 Hz), 1.57 (br s, 1H, OH), 1.99 (m, 3H), 2.28 (s, 3H), 3.99 (m, 2H), 6.71 (d, 1H, $J = 8.2$ Hz), 6.98 (d, 1H, $J = 8.2$ Hz), 7.21 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 8.6, 9.9, 20.6, 31.0, 33.3, 67.7, 71.1, 116.6, 125.8, 126.8, 129.5, 152.4. Anal. calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.51; H, 8.61.

6-Bromo-4-ethyl-3-methyl-benzopyran-4-ol (5e). Oil; IR (neat): $\nu = 3457$, 2971, 2938, 2881, 1485, 1461, 1136, 1089 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.71 (t, 3H, $J = 7.5$ Hz), 0.93 (d, 3H, $J = 6.9$ Hz), 1.90 (m, 2H), 2.11 (m, 1H), 2.3 (br s, 1H, OH), 3.86 (m, 1H), 4.24 (dd, 1H, $J = 3.5$, 10.9 Hz), 6.65 (d, 1H, $J = 8.7$ Hz), 7.20 (dd, 1H, $J = 2.3$, 8.7 Hz), 7.47 (d, 1H, $J = 2.16$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 8.4, 9.9, 31.2, 33.0, 67.9, 71.1, 112.5, 118.8, 128.3, 129.5, 131.6, 153.6. Anal. calcd. for $C_{12}H_{15}BrO_2$: C, 53.15; H, 5.58. Found: C, 52.92; H, 5.41.

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