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Isomerization of allylic alcohols into saturated carbonyls using phosphorus tribromide☆

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Abstract—Allylic alcohols **3**–**18** and **36** were efficiently isomerized to corresponding saturated carbonyls **19**–**34** and **37** in excellent yields under mild reaction conditions (5–9 min, 0 °C) using PBr_3.

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1. Introduction

The isomerization of allylic alcohols to saturated carbonyl compounds[1] is an important reaction in synthetic organic chemistry. Some of the well-known procedures for the transformation of allylic alcohols to saturated carbonyls are: (i) conventional two-step sequential oxidation and reduction reactions; (ii) a one-pot internal redox process mediated by various transition metal catalysts (iron,[2] rhodium,[3] ruthenium,[4] nickel,[5] iridium,[6] cobalt,[7] palladium,[8] platinum,[8] osmium[9] and molybdenum[10]); (iii) thermolysis of the allylic alcohol at 302–368 °C[11] and (iv) a controlled reaction with 2 equiv of *n*-BuLi.[12] A close analysis of all existing methods reveals that none is very practical. The conventional two-step oxidation and reduction procedures are tedious for complex molecules having multiple functional groups. In most cases, the one-pot isomerization requires relatively high quantities of an expensive catalyst leading to low turnover frequencies (TOF), turnover numbers (TON) and hence limits recycling. This coupled with the rather harsh reaction conditions (110–150 °C, 4–48 h, h*v*, etc.) has limited the use of most transition metal catalysts. On the other hand, heating allylic alcohols at >300 °C is very impractical and very few examples are known, which involve treatment of alcohols with *n*-BuLi to furnish saturated carbonyls.[13] Furthermore, the isomerization of allylic alcohols using known methods depends largely upon the substitution on the double bond. The reaction becomes more difficult as the number of substituents increases. A handful of examples are known for the transposition of trisubstituted and conjugated allylic alcohols into saturated carbonyls. Recently, formation of exocyclic olefins through phosphorus tribromide (PBr_3) treatment of allylic alcohols containing substituents with +I inductivity has been reported.[14] In continuation of this work, a new and highly efficient isomerization of allylic alcohols, containing substituents with moderate to good −I inductive effects into saturated carbonyls using PBr_3 is reported in this letter.

Ketone **1** was subjected to PBr_3 to furnish the corresponding bromo derivative **2**, which on reaction with *n*-butyllithium and aldehydes (R^1CHO, R^1 = alkyl, aryl, heteroaryl, etc.) at −78 °C furnished a set of allylic alcohols[15] **3**–**18**. On treatment of **3**–**18** with PBr_3 at 0 °C, the reaction proceeded smoothly and efficiently providing an excellent yield of saturated carbonyls **19**–**34** (Table 1). Selective isomerization of allylic alcohol **15**, having two types of double bond to the saturated carbonyl **31** was also observed (Scheme 1).

The versatility of the methodology for the isomerization of allylic alcohols was further demonstrated by the facile conversion of tris-allyl alcohol **36**, obtained from an *n*-BuLi exchange reaction of **2** and benzene-1,3,5-tricarbaldehyde **35**, into tris-ketone **37** (73%) (Scheme 2).

From close analysis of structures **19**–**34**, it is apparent that the isomerization of a diverse range of allylic alcohols obtained from reactions between bromo derivatives and a series of aldehydes was explored. A mechanistic hypothesis for the isomerization of the allylic alcohols

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Table 1. Isomerization of allylic alcohols **3**–**18** to saturated ketones **19**–**34**

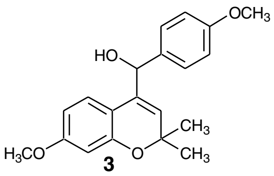
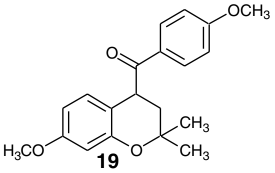
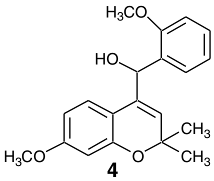
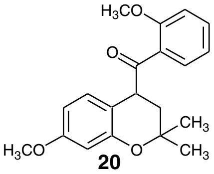
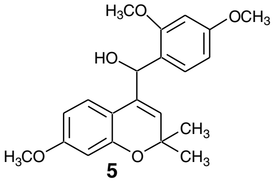
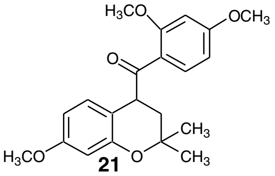
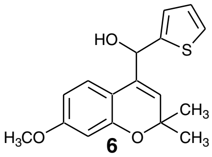
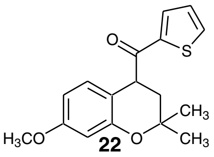
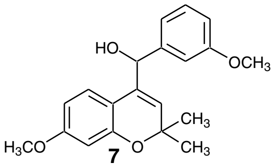
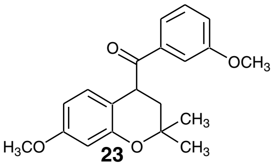
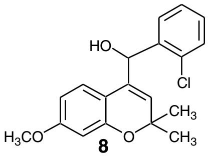
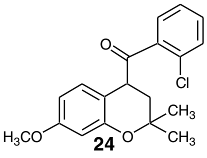
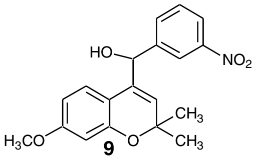
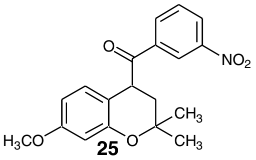
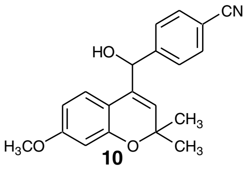
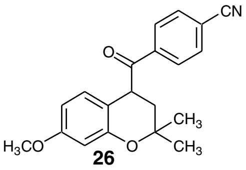
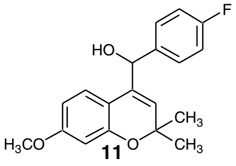
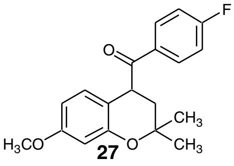
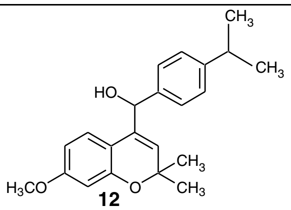
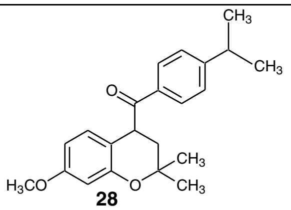
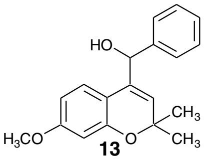
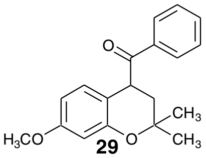
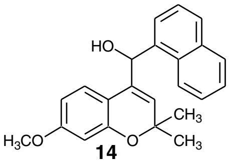
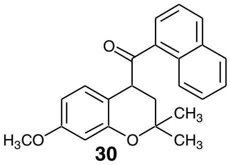
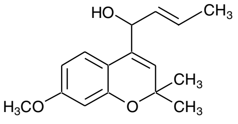
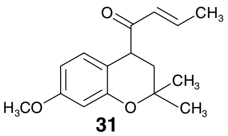
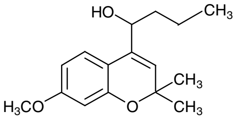
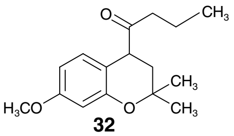
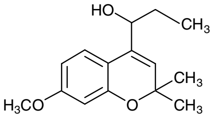
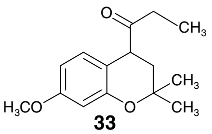
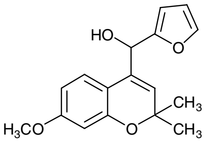
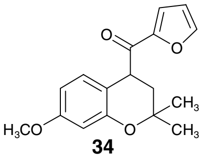
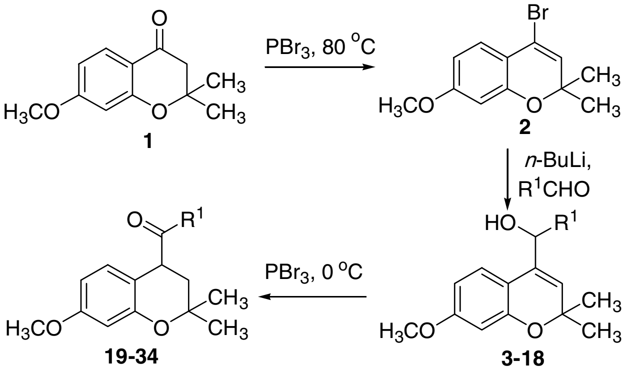
Entry	Allyl alcohol	Reaction conditions	Saturated ketone	Physical state, mp (°C)	Yield (%)
a	 **3**	0 °C, 6 min	 **19**	White solid, 105 °C	67[a]
b	 **4**	0 °C, 7 min	 **20**	Light yellow semi solid	65[b]
c	 **5**	0 °C, 6 min	 **21**	Yellow viscous oil	20[c]
d	 **6**	0 °C, 6 min	 **22**	Yellow oil	58[d]
e	 **7**	0 °C, 5 min	 **23**	Yellow viscous oil	78
f	 **8**	0 °C, 6 min	 **24**	Light yellow semi solid	60
g	 **9**	0 °C, 6 min	 **25**	Light yellow solid, 70 °C	82
h	 **10**	0 °C, 7 min	 **26**	Light brown semi solid	74
i	 **11**	0 °C, 5 min	 **27**	White crystalline solid, 81 °C	77

Table 1 (*continued*)

Entry	Allyl alcohol	Reaction conditions	Saturated ketone	Physical state, mp (°C)	Yield (%)
j	 **12**	0 °C, 6 min	 **28**	Yellow viscous oil	69
k	 **13**	0 °C, 8 min	 **29**	Light yellow viscous oil	73
l	 **14**	0 °C, 8 min	 **30**	White crystalline solid, 142 °C	75
m	 **15**	0 °C, 6 min	 **31**	Yellow viscous oil	69
n	 **16**	0 °C, 8 min	 **32**	Yellow viscous oil	63
o	 **17**	0 °C, 9 min	 **33**	Yellow viscous oil	61
p	 **18**	0 °C, 7 min	 **34**	Yellow viscous oil	67

[a] Along with exocyclic olefin[14] (15%).
[b] Along with exocyclic olefin (19%).
[c] Along with exocyclic olefin (56%).
[d] Along with exocyclic olefin (18%).

to saturated carbonyls using PBr_3 is shown in Scheme 3. The reaction of allylic alcohols **3**–**18** and **36** with PBr_3 could proceed through an intermediate **38** with elimination of HBr. The unsymmetrically substituted double bond in **38** is polarized due to the extended conjugation of the oxygen atom with the benzene ring. Addition of HBr onto the double bond of **38** follows Markovnikov's rule to furnish **39**. The H_a proton in **39** is acidic due to the presence of $OPBr_2$ and R^1 containing substituents with moderate to good −I inductive effects. Thus elimination of H_aBr from **39** furnished **40**. Finally hydrolysis of **40** would give **41**, which could tautomerise to the saturated carbonyls **19**–**34** and **37** (Scheme 3). The reaction was performed using PBr_3/Et_3N but did not yield any



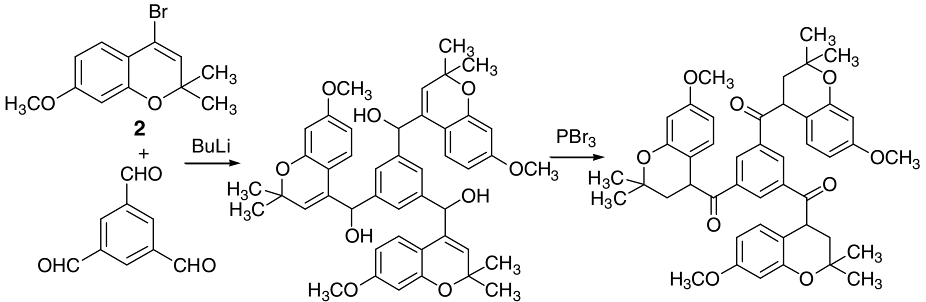
Scheme 1. Transformation of allylic alcohols **3**–**18** to saturated carbonyls **19**–**34** by PBr_3.

characterizable product. This suggests that the trapping of HBr by Et_3N eliminates the HBr required for the isomerization. Treatment of the allylic alcohol **11** with HBr/AcOH, HCl, AcOH and TFA was investigated. While **11** was recovered back after AcOH and TFA treatment, it furnished ketone **27** through very slow conversion in HBr/AcOH. Under HCl conditions, no characterizable product was obtained. This could be due to the fact that the H_a proton adjacent to $OPBr_2$ in **39** is very acidic and facilitates the elimination of H_aBr from **39** to give carbonyls. Incorporation of deuterium in place of H_a did not yield any deuteriated saturated ketones. Thus, the reaction did not proceed through 1,3-migration of H_a onto the double bond of **3**–**18** and **36** as in transition metal mediated isomerization.[1]

In conclusion, we have reported a new, highly efficient isomerization of abundantly available biologically important[15a,c] substituted allylic alcohols into their corresponding saturated carbonyls in excellent yields at 0 °C using PBr_3. It comprises only a single, instantaneous (5–9 min) step and hence is superior to known procedures. No highly expensive organometallic was used for this transformation. A remarkably simple route to the symmetric, polycyclic tris-ketone **37**, which is inaccessible by other means, was also accomplished using this methodology. The methodology provides a new dimension for the isomerization of allylic alcohols into saturated carbonyls.

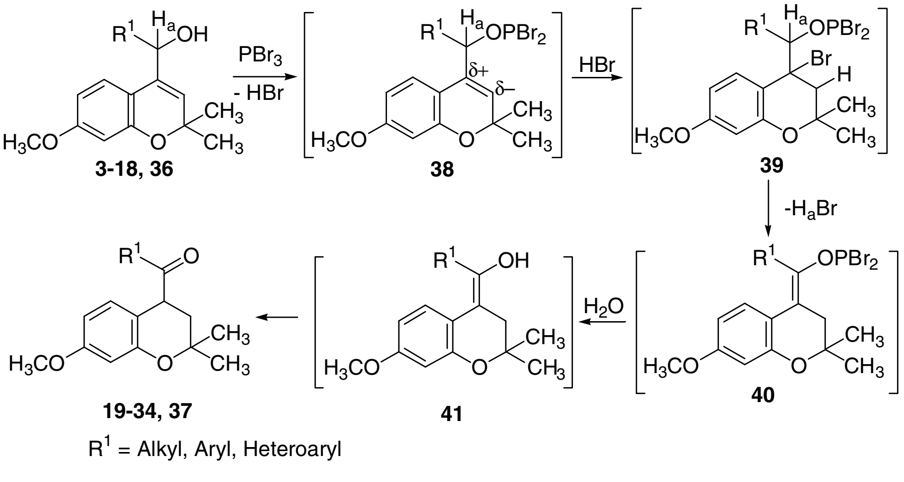
2. Typical procedure for 19–34

To a solution of carbinol **3**–**18** {0.100 g (1 equiv)} in dry benzene (2.5 mL) at 0 °C was added PBr_3 (1.5 equiv) and the mixture was stirred at room temperature. After completion of reaction, monitored using thin



35 **36** **37**

Scheme 2. Transformation of tris-allylic alcohol **36** to tris-ketone **37**.



3-18, 36 **38** **39** **40** **41** **19-34, 37**

R^1 = Alkyl, Aryl, Heteroaryl

Scheme 3. Plausible reaction mechanism for the transformation.

layer chromatography (TLC), the reaction mixture was poured into ice-cold water and extracted with ethyl acetate. Column chromatography of the crude product using silica gel (ethyl acetate/hexane) furnished compounds **19**–**34**.

2.1. (4-Fluorophenyl)-(7-methoxy-2,2-dimethylchroman-4-yl)-methanone 27

IR (KBr): 2975, 1683, 1617, 1596, 1504, 1161, 845 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.90–7.83 (m, 2H, Ar*H*), 7.06 (t, 2H, Ar*H*), 6.68 (d, 1H, $J = 8.7$, Ar*H*), 6.34–6.29 (m, 2H, Ar*H*), 4.56–4.51 (m, 1H, ArC*H*), 3.66 (s, 3H, OCH_3), 2.06–1.96 (m, 2H, $ArCHCH_2$), 1.35 {s, 3H, $C(CH_3)_2$}, 1.26 {s, 3H, $C(CH_3)_2$}; ^{13}C NMR (50 MHz, $CDCl_3$): 200.1, 160.2, 155.1, 133.1, 132.1, 129.8, 116.4, 116.0, 111.7, 108.1, 102.8, 74.8, 55.6, 42.7, 37.9, 29.8, 24.8. MS (FAB): *m*/*z* (%): 315 (70, $[M^+{+}H]$), 191 (100, $[M^+{-}OC_7H_4F]$). Anal. Calcd for $C_{19}H_{19}FO_3$: C, 72.60; H, 6.09. Found: C, 72.63; H, 6.13.

2.2. (7-Methoxy-2,2-dimethylchroman-4-yl)-naphthalen-2-yl-methanone 30

IR (KBr): 2976, 1674, 1593, 1351, 1159, 776 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.42–8.37 (m, 1H, Ar*H*), 8.00 (d, 1H, $J = 8.2$, Ar*H*), 7.92–7.80 (m, 2H, Ar*H*), 7.59–7.46 (m, 3H, Ar*H*), 6.98 (d, 1H, $J = 8.2$, Ar*H*), 6.49–6.43 (m, 2H, Ar*H*), 4.78–4.69 (m, 1H, ArC*H*), 3.76 (s, 3H, $-OCH_3$), 2.13–2.03 (m, 2H, $ArCHCH_2$), 1.39 {s, 3H, $C(CH_3)_2$}, 1.30 {s, 3H, $C(CH_3)_2$}; ^{13}C NMR (50 MHz, $CDCl_3$): 205.4, 160.3, 155.2, 136.9, 134.4, 132.9, 130.9, 130.3, 128.8, 128.4, 127.2, 127.0, 126.0, 124.8, 111.7, 108.0, 102.7, 74.5, 55.6, 45.3, 37.6, 29.6, 25.1. MS (FAB): *m*/*z* (%): 347 (90, $[M^+{+}H]$), 191 (100, $[M^+{-}COC_{10}H_7]$). Anal. Calcd for $C_{23}H_{22}O_3$: C, 79.74; H, 6.40. Found: C, 79.77; H, 6.48.

2.3. 1-(7-Methoxy-2,2-dimethylchroman-4-yl)-butan-1-one 32

IR (Neat): 2971, 1705, 1618, 1504, 1163, 1128, 758 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.79 (d, 1H, $J = 8.5$, Ar*H*), 6.48–6.38 (m, 2H, Ar*H*), 3.83–3.87 (m, 1H, ArC*H*), 3.75 (s, 3H, OCH_3), 2.37 (t, 2H, $-COCH_2CH_2CH_3$), 1.95 (d, 2H, $J = 8.9$, $ArCHCH_2$) 1.65–1.54 (m, 2H, $COCH_2CH_2CH_3$), 1.54 {s, 3H, $C(CH_3)_2$}, 1.24 {s, 3H, $C(CH_3)_2$}, 0.87 (t, 3H, $COCH_2CH_2CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): 212.2, 160.4, 155.0, 129.7, 110.8, 108.0, 102.7, 74.3, 55.5, 47.8, 41.5, 36.6, 29.8, 24.5, 17.7, 14.1. MS (FAB): *m*/*z* (%): 263 (40, $[M^+{+}H]$), 191 (100, $[M^+{-}COCH_2CH_2CH_3]$). Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.29; H, 8.47.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.12.046.

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