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A new strategy for the synthesis of aryl- and heteroaryl-substituted exocyclic olefins from allyl alcohols using PBr_3

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Abstract—Treatment of aryl and heteroaryl substituted allyl alcohols **7**–**14** with phosphorus tribromide at 0 °C furnished a new series of substituted exocyclic olefins **15**–**22** in good yields. The +I inductive effect of substituents on the aryl group is described.

Exocyclic olefins, particularly aryl-substituted examples are found in the structures of a variety of interesting natural and unnatural products.[1] For example, prostacyclin and carbaprostacyclin analogs such as **1** demonstrate antihypertensive and platelet aggregation inhibiting activity,[2] while enamide **2** serves as a key intermediate in the synthesis of a variety of isoquinoline alkaloids.[3] On the other hand, cynobacterin **3** is an antibiotic isolated from *Cynobacterium scytonema hofmanni*[4] (Fig. 1). While different methods are known for the synthesis of exocyclic olefins,[5] strategies for the synthesis of aryl substituted ones are scarce.[6]

A convenient synthesis of substituted 1-aryl methylnaphthalenes using phosphorous trihalide[7a,b,c] was recently reported by our group. It was observed that transforming the hydroxyl functionality in allyl alcohols **4** into a leaving group ($OPBr_2$) enforced aromatization in the dihydronaphthalene ring to furnish arylmethylnaphthalenes **6**. In continuation of our work, we were interested to observe the effect of a heteroatom substituent on the dihydronaphthalene ring on product formation and report our results herein (Scheme 1).

Thus, allyl alcohols **7**–**14** were synthesized from 2,2-dimethyl-7-methoxy-4-chromanone via a two-step sequence of reactions in 50–60% yields.[8] When allyl alcohols **7**–**14** were reacted with PBr_3 at 0 °C, the reaction proceeded smoothly providing moderate to good yields of exocyclic olefins **15**–**22** (Table 1). From close analysis of the percentage yields of the olefins, it was clear that the reaction was dependent on the +I inductive effect of the substituent at R^1. Increasing the number of OCH_3 groups and incorporation of $N(CH_3)_2$ groups on R^1 improved the yield of the reaction. Compounds **7** and **8** having one OCH_3 group furnished olefins **15** and **16** in 15% and 19% yields whereas allyl alcohols **9** and **10** having multiple OCH_3 groups gave 56% and 65% yields, respectively. Allyl alcohol **14** possessing an $N(CH_3)_2$ group (high +I effect) gave a good yield (67%) of the exocyclic olefin **22** (Scheme 1).

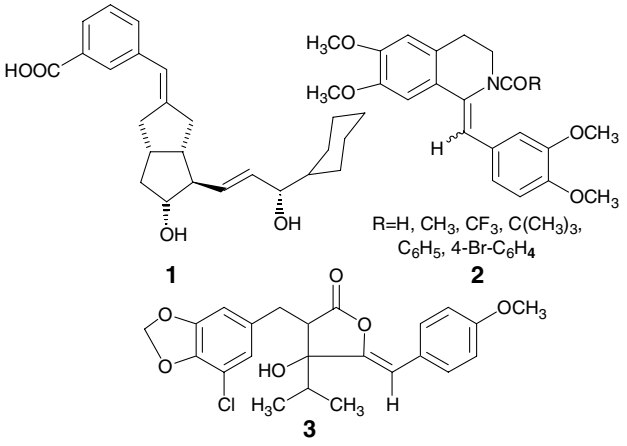

Figure 1. Structures of some bioactive aryl-substituted exocyclic olefins.

Keywords: Aryl-substituted exocyclic olefin; Phosphorous tribromide; Allyl alcohol.
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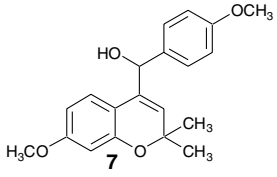
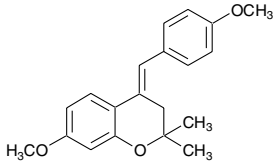
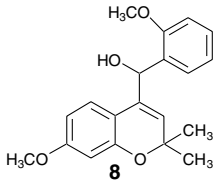
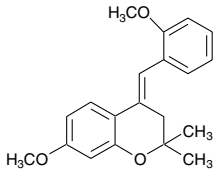
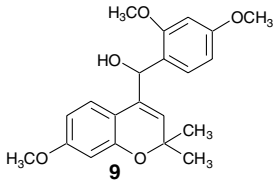
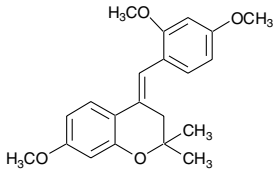
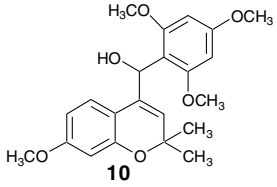
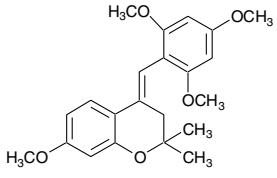
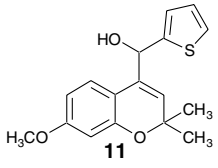
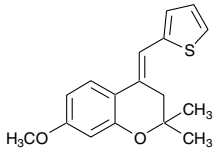
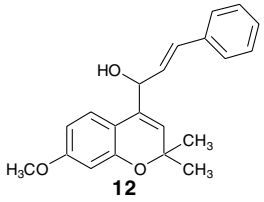
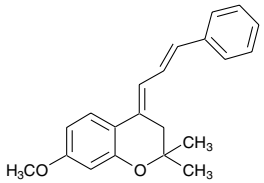
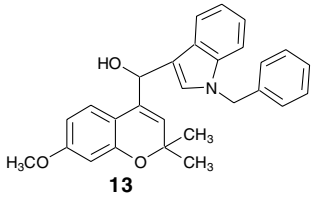
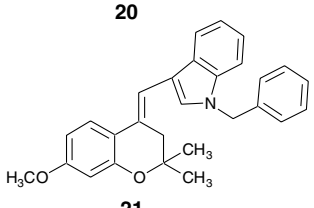
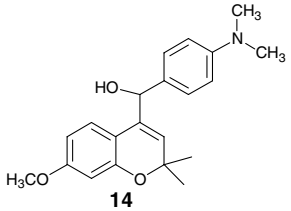
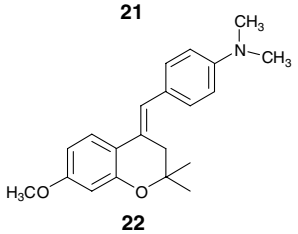
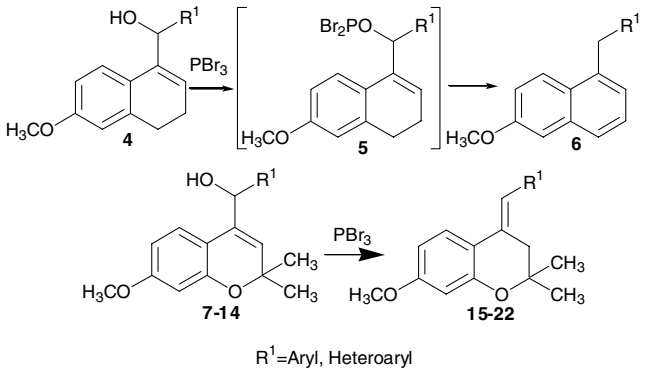
Table 1. Synthesis of aryl- and heteroaryl-substituted exocyclic olefins **15**–**22**

Entry	Allyl alcohol	Reaction conditions	Exocyclic olefin	Physical state, mp (°C)	Yield (%)
a	 **7**	0 °C, 5 min	 **15**	White solid, 97 °C	15
b	 **8**	0 °C, 7 min	 **16**	Yellow viscous oil	19
c	 **9**	0 °C, 6 min	 **17**	White solid, 150 °C	56
d	 **10**	0 °C, 8 min	 **18**	White solid, 150 °C	65
e	 **11**	0 °C, 6 min	 **19**	White solid, 105 °C	18
f	 **12**	0 °C, 5 min	 **20**	Yellow viscous oil	25
g	 **13**	0 °C, 6 min	 **21**	Yellow viscous oil	32
h	 **14**	0 °C, 6 min	 **22**	Yellow solid, 120 °C	67

The reaction can be thought to proceed via the formation of an intermediate **23**, formed from the reaction of allyl alcohols **7**–**14** with PBr_3 followed by elimination of HBr. The unsymmetrically substituted double bond



Scheme 1. Transformation of allyl alcohols **7**–**14** to exocyclic olefins **15**–**22** by PBr_3.

in **23** is polarized due to extended conjugation of the oxygen atom with the benzene ring. Addition of HBr onto the double bond of **23** follows Markovnikov's rule to furnish **24**. Finally, elimination of $POBr_3$ gave the exocyclic olefins **15**–**22** (Scheme 2). The extent of the +I inductive effect of substituents [2,4,6-OCH_3, $N(CH_3)_2$] at R^1 increases the probability of the $POBr_3$ leaving and thus furnishes improved yields of the olefins **18** (65%) and **22** (67%) from allyl alcohols **10** and **14**, respectively.

In conclusion, we have demonstrated that a new series of exocyclic olefins **15**–**22** can be easily synthesized from allyl alcohols **7**–**14** using PBr_3 as an inexpensive reagent. The method involves formation of olefins under mild conditions (0 °C, 5–8 min). In the reaction of allyl alcohols with PBr_3, the +I inductive effect of substituents on the aryl ring is described. Further work on the effect of other substituents on the aryl ring is currently underway.

Typical procedure for **15**–**22**: To a solution of carbinol **7**–**14** {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 was checked through thin layer chromatography (TLC), the mixture was poured into ice-cold water and extracted with ethyl acetate. Column chromatography of the crude product over silica gel (ethyl acetate/hexane) furnished compounds **15**–**22.**

4-(2,4-Dimethoxy-benzylidine)-7-methoxy-2,2-dimethyl-chroman **17**: IR (KBr): 2928, 1612, 1505, 1462, 1288, 1209, 1159, 1041, 760 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ 7.49 (d, 1H, $J = 8.7$ Hz, Ar*H*), 7.04–6.99 (m, 1H, Ar*H*) 6.94 (s, 1H, =C*H*-Ar), 6.41 (m, 3H, Ar*H*), 6.30 (m, 1H, Ar*H*), 3.75 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 2.56 (s, 2H, $ArCCH_2$), 1.20 {s, 6H, $C(CH_3)_2$}.

^{13}C NMR (50 MHz, $CDCl_3$): 160.8, 160.2, 159.2, 154.6, 131.2, 128.9, 125.6, 119.8, 116.9, 108.3, 104.2, 101.8, 98.9, 75.7, 55.9, 55.7, 38.0, 28.5, 27.1.

MS (FAB): *m*/*z*%: 340 (100, $[M^+]$), 325 (60, $[M^+-CH_3]$).

Anal. $C_{21}H_{24}O_4$; Calcd: C, 74.09; H, 7.11; Found: C, 74.12; H, 7.18.

7-Methoxy-2,2-dimethyl-4-(2,4,6-trimethoxy-benzylidene)-chroman **18**: IR (KBr): 2930, 1608, 1206, 1127, 761 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ 7.59 (d, 1H, $J = 8.7$Hz, Ar*H*), 6.65 (s, 1H, =C*H*Ar), 6.56 (dd, 1H,$J_1 = 8.5$Hz, $J_2 = 2.5$Hz, Ar*H*), 6.36 (d, 1H, $J = 2.6$Hz, Ar*H*), 6.17 (s, 2H, Ar*H*), 3.84 (s, 3H, OCH_3), 3.77 (s, 9H, OCH_3), 2.29 (s, 2H, $ArCCH_2$), 1.29 {s, 6H, $C(CH_3)_2$}.

^{13}C NMR (50 MHz, $CDCl_3$): 160.8, 159.2, 154.5, 131.2, 125.8, 115.9, 112.8, 108.6, 108.0, 101.8, 91.1, 76.0, 56.1, 55.7, 39.0, 27.1.

MS (FAB): *m*/*z* (%): 370 (80, $[M^+]$), 355 (100, $[M^+-CH_3]$).

Anal. $C_{22}H_{26}O_5$; Calcd: C, 71.33; H, 7.07; Found: C, 71.39; H, 7.08.

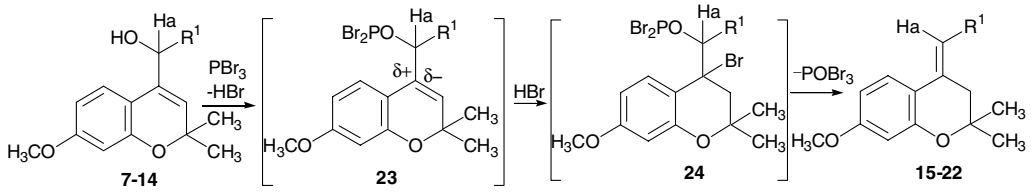
7-Methoxy-2,2-dimethyl-4-thiophen-2-ylmethylene-chroman **19**: IR (KBr): 2962, 1598, 1381, 1162, 1351, 1162, 707 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ 7.53 (d, 1H, $J = 8.8$Hz, Ar*H*), 7.28–7.24 (m, 1H, Ar*H*), 7.12 (s, 1H, —C*H*=C), 7.07–7.03 (m, 2H, Ar*H*), 6.52 (dd, 1H, $J_1 = 8.8$ Hz, $J_2 = 2.6$Hz, Ar*H*), 6.39 (s, 1H, $J = 2.6$ Hz, Ar*H*), 3.79 (s, 3H, –OCH_3), 2.86 (s, 2H, $ArCCH_2$), 1.35 {s, 6H, $C(CH_3)_2$}.

^{13}C NMR (50 MHz, $CDCl_3$): 161.3, 155.0, 141.2, 129.4, 127.7, 127.5, 125.1, 125.0, 114.1, 108.6, 102.2, 71.2, 55.7, 38.2, 27.2.

MS (FAB): *m*/*z* (%): 286 (100, $[M^{+1}]$), 271 (30, $[M^+ CH_3]$).

Anal. $C_{17}H_{18}O_2S$; Calcd: C, 71.30; H, 6.34; Found: C, 71.35; H, 6.33.



Scheme 2. Possible reaction mechanism.

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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.2005.10.081.

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