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Mild and practical stereoselective synthesis of (*Z*)- and (*E*)-allyl bromides from Baylis–Hillman adducts using Appel agents (PPh_3/CBr_4): a facile synthesis of semiplenamides C and E ☆

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ABSTRACT

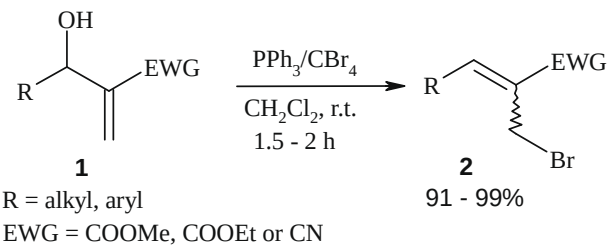
Appel agents (PPh_3/CBr_4) have been utilized for high-yielding stereoselective synthesis of (*Z*)- and (*E*)-allyl bromides from Baylis–Hillman adducts at room temperature. The method has been applied for the synthesis of naturally occurring bioactive fatty acid amides, semiplenamides C and E.

Baylis–Hillman adducts are important precursors for stereoselective synthesis of various functionalized molecules.[1] The allyl halides derived from these adducts have been employed for the synthesis of several bioactive compounds and their analogues such as α-methylene-γ-butyrolactones, α-alkylidene-β-lactams and flavonoids.[2] The conversion of the Baylis–Hillman adducts into their corresponding allyl bromides has generally been carried out by using a strong acid ($HBr–H_2SO_4$)[2b] or a metal halide (NaBr, LiBr, $CuBr_2$ or $MgBr_2$).[3] Some other mild methods using alternative reagents (PBr_3, PPh_3/NBS, HBr/SiO_2, PPh_3/Br_2 and DMS/NBS)[4] have also been developed to carry out this conversion. Herein, we wish to report the application of Appel agents (PPh_3/CBr_4)[5] for this conversion under very mild and metal-free conditions.

In connection to our works[6] on the Baylis–Hillman adducts, we have observed that the treatment of these adducts (**1**) with PPh_3/CBr_4 in CH_2Cl_2 afforded the corresponding allyl bromides (**2**) in high yields at room temperature (Scheme 1).

A series of allyl bromides were prepared from different Baylis–Hillman adducts containing both ester (–COOMe, –COOEt) and nitrile moieties (Table 1). The conversion was complete within 1.5–2 h and the products were formed in excellent yields (91–99%). The adducts derived from various aliphatic as well as aromatic aldehydes underwent the present conversion smoothly. The aromatic aldehydes containing both electron-donating and electron-withdrawing groups were used for the preparation of Baylis–Hillman adducts. Several functionalities such as halogen, nitro and ether groups remained unaffected. The structures of the products were settled from their spectral (IR, ^1H and ^{13}C NMR and MS) and analytical data.

The present conversion is highly stereoselective. The allyl bromides with ester moieties were obtained with (*Z*)-configuration as the sole products while those with nitrile group were formed with (*E*)-configuration as the major products (Table 1). The ratio of the (*Z*)- and (*E*)-isomers was determined from the ^1H NMR spectra of the crude products. The ^1H NMR spectra of the *E* and *Z*-isomers are according to the ones reported in the literature.[3d] These reported chemical shift values were helpful to determine the stereochemistry of the prepared allyl bromides.



Scheme 1.

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Table 1
Synthesis of allyl bromides using PPh_3/CBr_4[a]

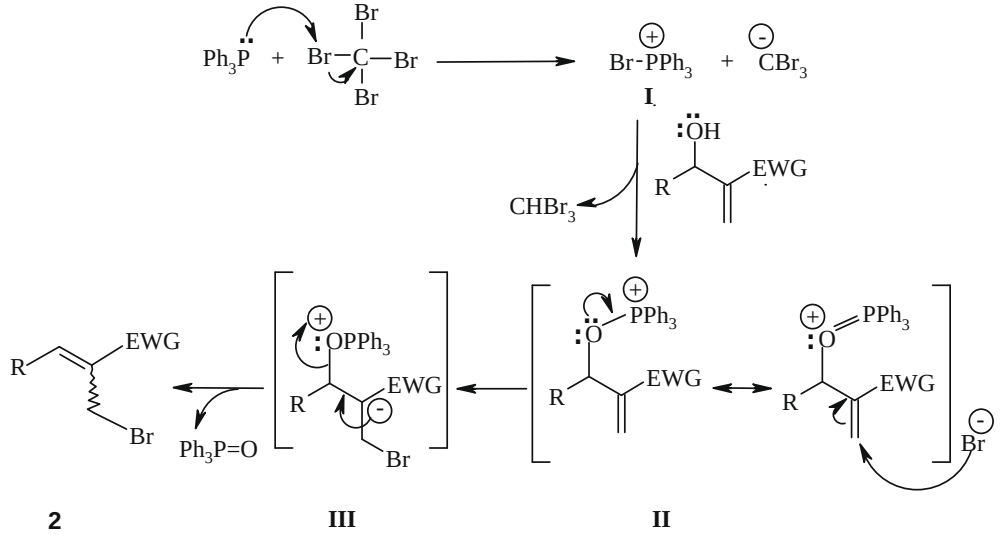
Entry	R	EWG	Product[b]	Time (h)	Yield (%)	*Z*:*E*[c]
a	C_6H_5	COOMe	**2a**	1.5	96	100:0
b	4-Cl–C_6H_4	COOMe	**2b**	1.5	97	100:0
c	4-MeO–C_6H_4	COOMe	**2c**	1.5	99	100:0
d	4-NO_2–C_6H_4	COOMe	**2d**	2.0	91	100:0
e	3-NO_2–C_6H_4	COOMe	**2e**	2.0	93	100:0
f	CH_3CH_2	COOMe	**2f**	1.5	97	100:0
g	$(CH_3)_2CH$	COOMe	**2g**	1.5	97	100:0
h	$H_3C(CH_2)_3CH_2$	COOMe	**2h**	1.5	97	100:0
i	$H_3C(CH_2)_5CH_2$	COOMe	**2i**	1.5	97	100:0
j	4-MeO–C_6H_4	COOEt	**2j**	1.5	99	100:0
k	4-$(CH_3)_2CH$–C_6H_4	COOEt	**2k**	1.5	98	100:0
l	$H_3C(CH_2)_{11}CH_2$	COOEt	**7**	1.5	98	100:0
m	$H_3C(CH_2)_{13}CH_2$	COOEt	**8**	1.5	98	100:0
n	$H_3C(CH_2)_{15}CH_2$	COOEt	**2n**	1.5	98	100:0
o	C_6H_5	CN	**2o**	1.5	94	6:94
p	3-NO_2–C_6H_4	CN	**2p**	2.0	92	10:90
q	4-Cl–C_6H_4	CN	**2q**	1.5	95	7:93

[a] Experimental conditions: Baylis–Hillman adduct **1** (1 mmol), PPh_3 (2 mmol), CBr_4 (2 mmol), CH_2Cl_2 (10 mL) and the reaction mixture were stirred at room temperature.
[b] The structures of the products were settled from their spectral (IR, ^1H and ^{13}C NMR and MS) and analytical data.
[c] Determined from the ^1H NMR spectra of the crude products.

The mechanism of the conversion involves the interaction of PPh_3 with CBr_4 to form the intermediate **I** which reacts with a Baylis–Hillman adduct to produce the oxyphosphonium intermediate **II**. Bromide ion then attacks this intermediate to afford the allyl bromide and Ph_3PO via a general transition state **III** (Scheme 2).

The configuration of **2** can possibly be rationalized by considering the transition state models **A**–**C** (Fig. 1). Model **A** is more favoured than **B** when EWG is an ester and (*Z*)-products are formed predominantly. On the other hand, model **C** is more favoured than **A** when EWG is –CN (which is linear) and thus (*E*)-compounds are the major products.

The present method has been applied for the synthesis of two naturally occurring fatty acid amides, semiplenamides C (**3**) and E (**4**).[7] These two amides were isolated from the marine cyanobacterium *Lyngia semiplena* and were shown to display toxicity towards the brine shrimp model system. For the synthesis of **3** and **4,** the Baylis–Hillman adducts **5** and **6** (derived from tetradecanal and hexadecanal, respectively, and ethyl acrylate) were used as starting materials (Scheme 3). These adducts on treatment with PPh_3/CBr_4 in CH_2Cl_2 afforded the corresponding allyl bromides **7** and **8** which were subsequently reduced with Zn/CH_3COOH to afford the esters **9** and **10**, respectively.[8] These esters were then hydrolyzed with 85% methanolic KOH to form the corresponding acids **11** and **12** which on treatment with (*S*)-alaninol in the presence of HOBt (1-hydroxybenzotriazole hydrate), DIEA (diisopropylethylamine) and EDCI (*N*-(3-dimethylaminopropyl)-*N*′ethylcarbodiimide hydrochloride) afforded the amides **3** and **13**, respectively.[9] Compound **13** was further acetylated with acetic anhydride using pyridine and DMAP to furnish product **4**. The physical (mp and $[\alpha]_D$) and spectral data suggested that the amides **3** and **4** were identical to the naturally occurring semiplenamides C and E, respectively.



Scheme 2. A plausible reaction mechanism.

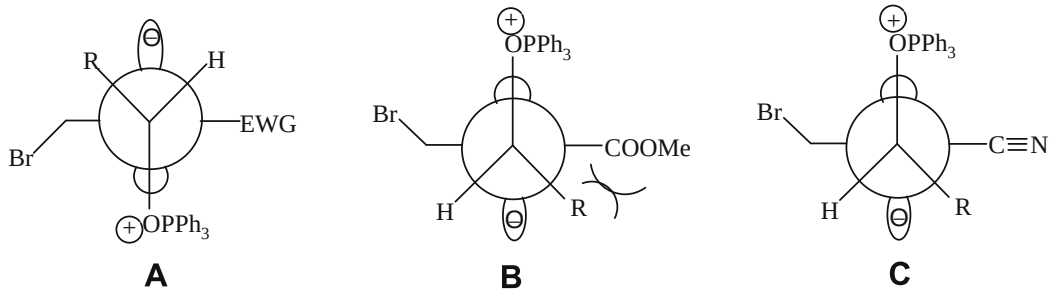
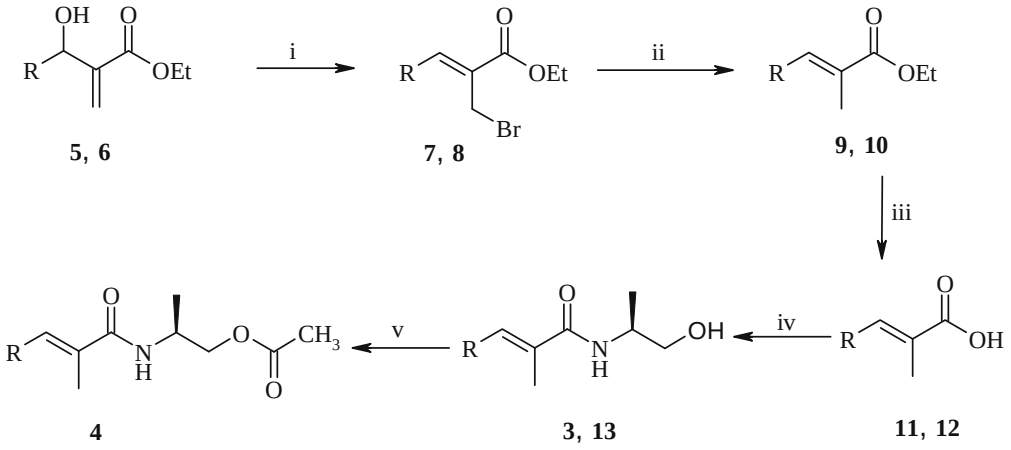


Figure 1. Conformational transition-state analysis for the rationalization of the observed stereoselectivity in the reaction leading to the allyl bromides **2**.



Scheme 3. Synthesis of Semiplenamides C and E. Reagents and conditions: (i) PPh_3/CBr_4, CH_2Cl_2, rt, 1.5 h, (**7**, **8** 98%); (ii) Zn (3 equiv), CH_2Cl_2, rt, 30 min, then CH_3COOH (slowly), 0 °C; rt, 30 min, (**9** 89%, **10** 87%); (iii) 85% methanolic KOH, rt, 5 h, (**11** 84%, **12** 83%); (iv) (*S*)-alaninol, HOBt, DIEA, EDCI, 0 °C, 15 min; rt, 24 h, (**3** 81%, **13** 79%); (v) Ac_2O, Py, DMAP, rt, 4 h, 92%

In conclusion, we have developed a simple, mild and efficient practical method for the stereoselective synthesis of (*Z*)- and (*E*)-allyl bromides starting from Baylis–Hillman adducts by treatment with Appel agents (PPh_3/CBr_4) at room temperature. The method has successfully been applied for the facile synthesis of two naturally occurring bioactive fatty acid amides, semiplenamides C and E.

General experimental procedure: To a stirred solution of Baylis–Hillman adduct **1** (1 mmol) and PPh_3 (2 mmol) in dry CH_2Cl_2 (10 ml), CBr_4 (2 mmol) was added under nitrogen atmosphere. The mixture was stirred at room temperature and the reaction was monitored by TLC. After completion, the reaction mixture was quenched with cold water (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography over silica gel using hexane–EtOAc (19:1–9:1) as eluent to yield the corresponding allyl bromide **2**.

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Supplementary data

Copies of ^1H and ^{13}C NMR spectra for selected compounds and spectral (IR, ^1H and ^{13}C NMR and MS) and analytical data of the unknown allyl bromides (**2g**, **2h**, **7**, **8**, **2n**, **2q**) and of all the products involved in the synthesis of semiplenamides C and E.. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.132.

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