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A Rapid and Efficient Synthesis of Allyl Iodides from Baylis–Hillman Adducts: A Facile Synthesis of Semiplenamide D[1]

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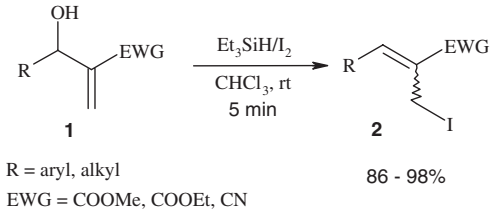
Treatment of Baylis–Hillman adducts with Et_3SiH/I_2 in $CHCl_3$ at room temperature afforded the (*Z*)- and (*E*)-allyl iodides in stereoselective manner. The products are formed in excellent yields within 5 min. The method has successfully been utilized for synthesis of natural bioactive fatty acid amide, semiplenamide D.

Baylis–Hillman adducts[2] are valuable precursors for stereoselective synthesis of different multifunctional molecules.[3] The substituted allyl halides derived from these adducts are employed for synthesis of various bioactive natural products and their analogs such as flavonoids,[4a] α-methylene-γ-butyrolactones,[4b] and α-alkylidene-β-lactams.[4c] However, the methods of preparation of allyl iodides from Baylis–Hillman adducts are limited. Previously some reagents (such as I_2/Sm,[5a] I_2/PMHS,[5b] HI/H_3PO_4,[5c] NaI/KSF,[5d] NaI/TMSCl,[5e] and LiI/$NaHSO_4.SiO_2$[5f]) were employed for preparation of these compounds starting from the adducts and their derivatives. Most of the methods using these reagents are associated with certain drawbacks including long reaction times, use of a strong acid, low selectivity, and unsatisfactory yields.

In continuation of our work[5b,5f,6] on the Baylis–Hillman adducts we have observed that these compounds **1** can conveniently be converted into the corresponding allyl iodides **2** by treatment with Et_3SiH and I_2 in $CHCl_3$ at room temperature (Scheme 1).

Baylis–Hillman adducts having ester or nitrile moiety underwent the conversion smoothly and a series of allyl iodides were prepared (Table 1). The products were formed in excellent yields (86–98%) within 5 min. Previously allyl iodides were not prepared from Baylis–Hillman adducts so rapidly without using microwaves: this is a notable feature of the present method.[5] The adducts derived from both aromatic and aliphatic aldehydes afforded the allyl iodides in impressive yields. The aryl moiety in the adducts contained electron-donating as well as electron-withdrawing groups. Earlier some methods reported the preparation of allyl iodides containing only an aryl group.[5] Different functional groups such as halogen, ether, nitro, and ester groups remained here unchanged. The products were characterized from their spectral (^{1}H and ^{13}C NMR and MS) and analytical data.[7]



Scheme 1.

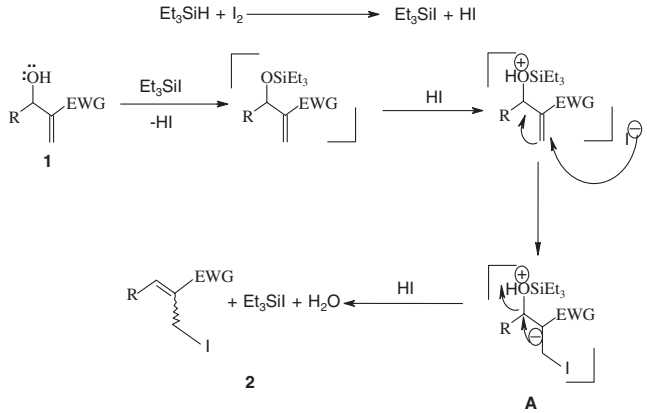
The allyl iodides were formed in stereoselective manner. The compounds with an ester group were produced with (*Z*)-configuration and those having a nitrile group were formed with (*E*)-configuration. The ^{1}H NMR spectra of the products were used to establish their stereochemistry by comparison with reported data for known compounds.[5]

The mechanism of the present conversion involves the initial formation of HI (by interaction of Et_3SiH and I_2) which then attacks the Baylis–Hillman adduct to furnish the corresponding allyl iodide (Scheme 2).[4c,5f] The hydrogen-bonding interaction of the oxonium cation with enolate in the intermediate **A** (Scheme 2) explains the (*Z*)-selectivity of **2** containing an ester group while the absence of this interaction in the nitrile explains the (*E*)-selectivity of the derived product **2**.[6a]

Table 1. Synthesis of allyl iodides using $EtSiH_3/I_2$[a]

Entry	R	EWG	Product[b]	Yield/%[c]	*Z*:*E*[d]
a	C_6H_5	COOMe	**2a**	93	100:0
b	4-Cl-C_6H_4	COOMe	**2b**	97	100:0
c	3-NO_2-C_6H_4	COOMe	**2c**	96	100:0
d	CH_3CH_2	COOMe	**2d**	86	100:0
e	$(CH_3)_2CH$	COOMe	**2e**	97	100:0
f	$H_3C(CH_2)_3CH_2$	COOMe	**2f**	88	100:0
g	4-$(CH_3)_2CH$-C_6H_4	COOEt	**2g**	97	100:0
h	$H_3C(CH_2)_{11}CH_2$	COOEt	**2h**	98	100:0
i	$H_3C(CH_2)_{13}CH_2$	COOEt	**2i**	94	100:0
j	$H_3C(CH_2)_{15}CH_2$	COOEt	**2j**	95	100:0
k	C_6H_5	CN	**2k**	95	6:94
l	3-NO_2-C_6H_4	CN	**2l**	90	10:90
m	4-OMe-C_6H_4	CN	**2m**	91	7:93

[a]Experimental conditions: Baylis–Hillman adduct **1** (0.5 mmol), Et_3SiH (0.5 mmol), I_2 (0.5 mmol), $CHCl_3$ (10 mL) and the reaction mixture was stirred at room temperature for 5 min. [b]The structures of the products were settled from their spectral (^{1}H and ^{13}C NMR and MS) and analytical data. [c]Yield of the product after purification. [d]Determined from the ^{1}H NMR spectra of the crude products.



Scheme 2.

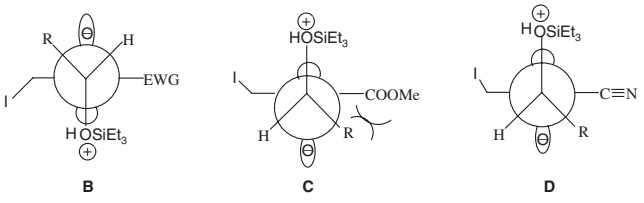
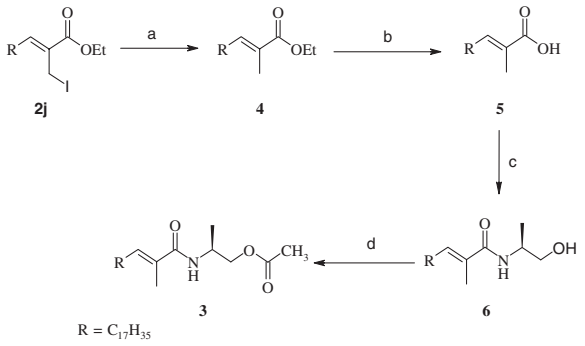


Figure 1.



Scheme 3. Reagents and conditions: (a) Zn (3 equiv), CH_2Cl_2, rt, 30 min, then CH_3OOOH (slowly), 0 °C–rt, 30 min, 84%; (b) 85% methanolic KOH, rt, 5 h, 82%; (c) (*S*)-alaninol, HOBt, DIEA, EDCI, 0 °C, 15 min, rt, 24 h, 80%; and (d) Ac_2O, Py, DMAP, rt, 4 h, 95%.

Earlier a combination of concentrated HI and concentrated H_3PO_4 was used for iodination of Baylis–Hillman adducts but the required times were high (6 days) and the yields were comparatively low.[5c]

The configuration of the allyl iodides **2** can possibly be rationalized by considering the transition state models **B**–**D** (Figure 1). Model **B** is more favored than **C** when EWG is an ester and allyl iodides with (*Z*)-configuration are produced. However, model **D** is more favored than **B** when EWG is nitrile (which is linear) and thus (*E*)-products are formed.

The present methodology has successfully been employed for the synthesis of natural fatty acid amide, semiplenamide D (**3**)[8] (Scheme 3). The compound was isolated from a marine cyanobacterium, *Lyngbya semiplena* and displayed toxicity in the brine shrimp model system. The allyl iodide **2j** (Table 1) produced from the Baylis–Hillman adduct derived from octadecanal was reduced with Zn/AcOH to form the ester **4**.[9] The ester was hydrolysed with 85% methanolic KOH to produce the corresponding acid **5**. The acid **5** was subsequently treated with (*S*)-alaninol in the presence of HOBT (1-hydroxybenzotriazole hydrate), DIPEA (diisopropylethylamine) and EDCI [*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride] to produce the amide **6**.[10] On acetylation with Ac_2O using pyridine and DMAP compound **6** afforded the product **3** whose physical and spectral data are identical to those of semiplenamide D.[8]

In conclusion, we have developed a highly efficient method for the synthesis of (*Z*)- and (*E*)-allyl iodides from Baylis–Hillman adducts by treatment with Et_3SiH/I_2 at room temperature. The mild reaction conditions, rapid preparation, operational simplicity, impressive stereoselectivity, and excellent yields are the advantages of the method. The method has been employed for the synthesis of natural bioactive fatty acid amide, semiplenamide D.

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References and Notes

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7 General experimental procedure: To a solution of Baylis–Hillman adduct (0.5 mmol) and Et_3SiH (0.5 mmol) in $CHCl_3$ (5 mL), iodine (0.5 mmol) was added. The mixture was stirred for 5 min when the reaction was complete. The solution was removed under vacuum and water (10 mL) was added to the residue. The mixture was extracted with EtOAc (3 × 10 mL) and the extract was dried and concentrated. The crude mass was subjected to column chromatography (silica gel, hexane–EtOAc) to obtain pure allyl iodide. The spectral and analytical data of some representative compounds are given below. **2d**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.88 (1H, t, $J = 7.0$ Hz), 4.12 (2H, s), 3.80 (3H, s), 2.25–2.19 (2H, s), 1.16 (3H, t, $J = 7.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.8, 142.2, 129.9, 52.0, 29.6, 21.8, 12.1; ESIMS: m/z 255 $[M + H]^+$, 127 $[M - I]^+$; Calcd for $C_7H_{11}IO_2$: C, 33.08; H, 4.36%. Found: C, 33.18; H, 4.36%. **2j**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.92 (1H, t, $J = 7.0$ Hz), 4.28 (2H, q, $J = 7.0$ Hz), 4.13 (2H, s), 2.19 (2H, q, $J = 7.0$ Hz), 1.60–1.48 (2H, m), 1.41–1.21 (31H, m), 0.89 (3H, t, $J = 7.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.9, 147.0, 130.5, 61.1, 31.9, 29.8, 29.6, 29.5, 29.3, 27.8, 14.1, 14.0; ESIMS: m/z 479 $[M + H]^+$; Calcd for $C_{23}H_{43}IO_2$: C, 57.73; H, 9.06%. Found: C, 57.77; H, 9.03%. **2l** (*E*): ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.39 (2H, d, $J = 8.0$ Hz), 7.90 (2H, d, $J = 8.0$ Hz), 7.31 (1H, s), 4.48 (2H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 146.8, 144.5, 140.4, 132.1, 124.5, 114.0, 112.2, 114.0, 29.3; ESIMS: m/z 315 $[M + H]^+$, 187 $[M - I]^+$; Calcd for $C_{10}H_7IN_2O_2$: C, 38.23; H, 2.25; N, 8.92%. Found: C, 38.32; H, 2.25; N, 8.95%. **3**: White solid, mp 97–99 °C, $[\alpha]_D^{25}$ −12.8 (*c* 0.3, $CHCl_3$). [lit.[6] $[\alpha]_D^{25}$ −10.6 (*c* 0.15, $CHCl_3$)]; IR: 3282, 1725, 1660, 1623, 1537, 1466 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.29 (1H, t, $J = 7.0$ Hz), 5.82 (1H, d, $J = 7.0$ Hz), 4.32 (1H, m), 4.20 (1H, dd, $J = 12.0$, 6.0 Hz), 4.02 (1H, dd, $J = 12.0$, 4.0 Hz), 2.13 (1H, q, $J = 7.0$ Hz), 2.10 (3H, s), 1.82 (3H, s), 1.48–1.25 (31H, m), 1.18 (3H, d, $J = 7.0$ Hz), 0.89 (3H, t, $J = 7.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.7, 169.4, 137.2, 130.5, 67.4, 45.0, 32.2, 30.2, 29.7, 29.6, 29.4, 28.6, 21.3, 20.7, 19.5, 15.1, 12.3; ESIMS: 424 $[M + H]^+$; HRESIMS: Calcd for $C_{26}H_{49}NO_3Na$: m/z 446.3610 $[M + Na]^+$; Found: m/z 446.3628.
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