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The Baylis–Hillman chemistry in aqueous media: a convenient synthesis of 2-methylenealkanoates and alkanenitriles

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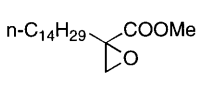
Abstract—A convenient, general and efficient synthesis of 2-methylenealkanoates and alkanenitriles is accomplished via the regioselective nucleophilic (S_N2') addition of hydride ion from $NaBH_4$ to (2*Z*)-2-(bromomethyl)alk-2-enoates and 2-(bromomethyl)alk-2-enenitriles respectively in the presence of DABCO in environment friendly aqueous media. Synthesis of two hypoglycemic agents is also described.

Development of simple and convenient methodology for the synthesis of 2-methylenealkanoates and alkanenitriles is an interesting problem in organic synthesis[1] because of their versatile applications as synthons in the synthesis of various biologically active molecules[2] and liquid crystalline polymers.[3] For example, methyl 2-tetradecyloxiranecarboxylate (methyl palmoxirate) (**1**) and ethyl 2-[6-(4-chlorophenoxy)hexyl]oxirane-2-carboxylate (Etomoxir) (**2**) have been found to be potent inhibitors of the fatty acid oxidation and oral hypoglycemic agents in mammals including human beings.[2] In recent years, the Baylis–Hillman reaction[4] has attracted the attention of organic chemists as it provides densely functionalized molecules which have been utilized in numerous synthetic transformations.[4–6] As a part of our research program on the Baylis–Hillman chemistry[6] and environment friendly chemistry,[7] we herein report a convenient synthesis of 2-methylenealkanoates and alkanenitriles via the regioselective nucleophilic addition (S_N2') of hydride ion from $NaBH_4$ to allyl bromides i.e. (2*Z*)-2-(bromomethyl)alk-2-enoates and 2-(bromomethyl)alk-2-enenitriles, derived from the Baylis–Hillman adducts, respectively, in the presence of DABCO in aqueous media.

Hoffmann and Rabe used superhydride ($LiBEt_3H$) for the conversion of methyl (2*Z*)-2-(bromomethyl)hex-2-enoate into methyl 2-methylenehexanoate (S_N2' product).[8] Corey, during his elegant synthesis of α-santalol, described the reaction of methyl (2*E*)-2-(bromomethyl)dec-2-enoate with $NaBH_4$ in DMSO to provide methyl 2-methylenedecanoate as a major (S_N2') product ($\approx 75\%$ yield) along with two other compounds in minor amounts ($\approx 10\%$ and $\approx 15\%$ yields).[9] Hall and coworkers employed sodium 9-cyano-9-hydrido-9-borabicyclo[3.3.1]nonane in HMPA for similar S_N2' transformation in the synthesis of liquid crystalline polymers, however they also obtained considerable amounts of S_N2 products.[3]

In connection with our ongoing research program in environment friendly chemistry[7] and sodium borohydride chemistry,[6c] we felt that if we can develop a general and convenient methodology for the synthesis of pure methyl 2-methylenealkanoates via the reduction of methyl (2*Z*)-2-(bromomethyl)alk-2-enoates with $NaBH_4$ in high yields under appropriate conditions in aqueous media, this methodology will be of high synthetic importance. Accordingly, we have first examined



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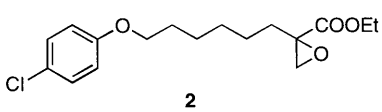

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Keywords: Baylis–Hillman chemistry; regioselectivity; 2-methylenealkanoates; alkanenitriles.

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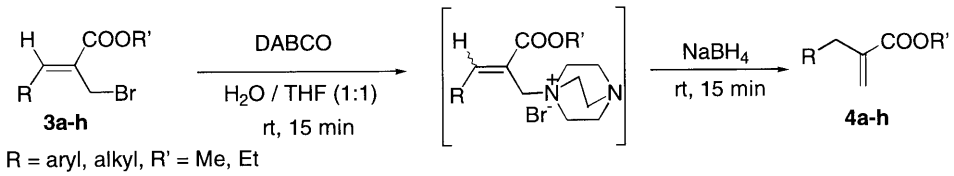
the reaction of methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (**3a**)[10] with sodium borohydride in water/THF medium under various conditions. The best results were obtained when methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (**3a**) (2 mM) was treated with DABCO (2 mM) in the presence of H_2O/THF (1:1) at room temperature for 15 minutes followed by the treatment with $NaBH_4$ (2 mM) for 15 minutes at room temperature, thus providing the required pure methyl 2-methylene-3-phenylpropanoate (**4a**) after usual work up followed by column chromatography (silica gel, 2% ethyl acetate in hexanes) in 83% yield.[11–13] Encouraged by this result, we have synthesized a variety of 2-methylenealkanoates (**4b–h**) in high yields from various (2*Z*)-2-(bromomethyl)alk-2-enoates (**3b–h**)[10] (Scheme 1, Table 1).

With a view to understanding the generality of this methodology, we have also transformed 2-(bromomethyl)alk-2-enenitriles (**5a–g**)[10] obtained from the corresponding Baylis–Hillman adducts i.e., 3-hydroxy-2-methylenealkanenitriles, into 2-methylenealkanenitriles (**6a–g**) in high yields (Scheme 2, Table 1).

We have successfully transformed 2-methylenealkanoates **4g–h** into the corresponding methyl 2-tetradecyloxirane-2-carboxylate (methyl palmoxirate) (**1**) and ethyl 2-[6-(4-chlorophenoxy)hexyl]oxirane-2-car-



Scheme 1.

Table 1. Synthesis of 2-methylenealkanoates (**4a–h**) and alkanenitriles (**6a–g**)[a,b]

Allyl bromide	R	EWG	Product	Yield[c] (%)
3a	Phenyl	COOMe	**4a**[d,e,12]	83
3b	4-Chlorophenyl	COOMe	**4b**[d]	87
3c	4-Methylphenyl	COOMe	**4c**[d]	80
3d	2-Chlorophenyl	COOMe	**4d**[d]	82
3e	2-Methylphenyl	COOMe	**4e**[d]	84
3f	*n*-Pentyl	COOMe	**4f**[d,e]	72
3g	*n*-Tridecyl	COOMe	**4g**	76
3h	5-(4-Chlorophenoxy)pent-1-yl	COOEt	**4h**[f]	73
5a	Phenyl	CN	**6a**[d,e,14]	82
5b	4-Chlorophenyl	CN	**6b**[d,e]	90
5c	4-Methylphenyl	CN	**6c**[d]	81
5d	2-Chlorophenyl	CN	**6d**[d]	85
5e	2-Methylphenyl	CN	**6e**[d]	87
5f	*n*-Pentyl	CN	**6f**[e]	74
5g	*n*-Tridecyl	CN	**6g**[f]	82

[a] All reactions were carried out on 2 mM scale of the allyl bromide with 2 mM of DABCO in H_2O/THF (1:1) at room temperature for 15 min followed by the treatment with $NaBH_4$ (2 mM) at room temperature for 15 min.

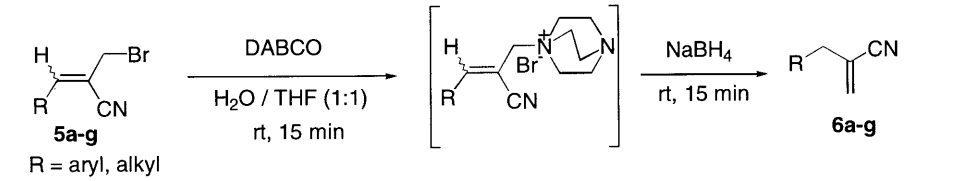
[b] All the products were obtained as colorless liquids and were characterized by IR, ^1H NMR (200 MHz), ^{13}C NMR (50 MHz) spectral data and elemental analyses.

[c] Isolated yields of the products after column chromatography (silica gel, 2% EtOAc in hexanes).

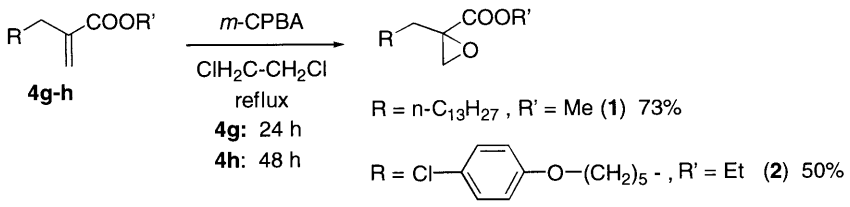
[d] Structure of these molecules was further confirmed by mass spectral analysis.

[e] These molecules are known in the literature.[1a,b,d–f,15]

[f] These reactions were carried out on 1 mM scale of the allyl bromide.



Scheme 2.



(1)

boxylate (Etomoxir) (**2**), important hypoglycemic agents (Eq. (1)).[16]

In conclusion, this methodology describes a convenient and general synthesis of 2-methylenealkanoates and alkanenitriles in environment friendly aqueous media, thus demonstrating the synthetic potential of Baylis–Hillman adducts.

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10. (2*Z*)-2-(Bromomethyl)alk-2-enoates and 2-(bromomethyl)-alk-2-enenitriles were prepared according to the literature procedure.[17] 2-(Bromomethyl)alk-2-enenitriles were obtained as mixtures of (*E*)- and (*Z*)-isomers which as such were used for reactions.
11. We have examined the reaction of **3a** with sodium borohydride in water/THF medium in the absence of DABCO. The reaction was very slow i.e. even after 16 hours at room temperature about 60% of the starting material remained intact, thus providing the desired product **4a** in about 26% yield only along with methyl α-methylcinnamate (≈ 14% yield) as evidenced by the ^{1}H NMR spectrum of the crude concentrated product.
12. **Spectral data for 4a:** IR (neat): 1722, 1631 cm^{-1}; ^{1}H NMR (200 MHz) ($CDCl_3$): δ 3.63 (s, 2H), 3.72 (s, 3H), 5.46 (s, 1H), 6.23 (s, 1H), 7.12–7.35 (m, 5H). ^{13}C NMR (50 MHz) ($CDCl_3$): δ 38.02, 51.72, 126.06, 126.29, 128.37, 128.96, 138.67, 140.15, 167.23; MS (*m*/*z*): 176 (M^+). Elemental analysis calculated for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86; found C, 74.72; H, 6.89.
13. DABCO-allyl bromide salt was isolated in the case of **3a**. ^{1}H and ^{13}C NMR spectral analysis indicates that this salt is a mixture of *E*- and *Z*-isomers in the ratio of ≈ 82:18.
14. **Spectral data for 6a:** IR (neat): 2224, 1622 cm^{-1}; ^{1}H NMR (200 MHz) ($CDCl_3$): δ 3.56 (s, 2H), 5.70 (s, 1H), 5.91 (s, 1H), 7.13–7.42 (m, 5H). ^{13}C NMR (50 MHz) ($CDCl_3$): δ 40.55, 118.33, 122.51, 127.23, 128.74, 130.87, 135.54; MS (*m*/*z*): 143 (M^+). Elemental analysis calculated for $C_{10}H_9N$: C, 83.88; H, 6.34, N, 9.78; found C, 83.60; H, 6.34, N, 9.83.
15. ^{1}H NMR spectral data of **4a** and **6a,f** are reported.[1b,d] Our ^{1}H NMR spectral data of these molecules are in agreement with the literature data.
16. ^{1}H NMR spectra of these compounds (**1** and **2**) are in agreement with literature data.[2a,c]
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