Pergamon

Tetrahedron Letters, Vol. 38, No. 12, pp. 2141-2144, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00266-9

The Friedel-Crafts Reaction of the Baylis-Hillman Adducts

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Abstract: A simple and convenient methodology for the stereoselective construction of 2-benzyl substituted trisubstituted olefins *via* sulfuric acid catalyzed Friedel-Crafts reaction of benzene with Baylis-Hillman adducts is described. © 1997 Elsevier Science Ltd.

The Baylis-Hillman reaction is an emerging carbon-carbon bond forming reaction providing synthetically useful molecules and is of current interest[1-5]. As a part of our research program on stereoselective synthesis, we have identified the Baylis-Hillman adducts as versatile intermediates for the stereodefined construction of trisubstituted olefins[5-11]. We have recently reported a stereoselective $AlCl_3$ promoted Friedel-Crafts reaction[12,13] of the acetates of Baylis-Hillman adducts with benzene to give 2-benzyl substituted functionalized olefins, which are otherwise difficult to synthesize[9]. However, in this reaction more than one equivalent of $AlCl_3$ is necessary to induce Friedel-Crafts reaction in acceptable yields[9] and in some cases undesirable side products are formed. Consequently a general method for the generation of allyl carbocation electrophiles without $AlCl_3$ would be highly desirable. We have therefore envisioned the possibility of utilizing the Baylis-Hillman adducts themselves as stereodefined β-electrophiles by using a catalytic amount of a strong protic acid. We herein report our results in this direction thus providing a simple stereoselective synthesis of [2*Z*]-2-benzylalk-2-enenitriles and methyl [2*E*]-2-benzylalk-2-enoates *via* the Friedel-Crafts reaction of 3-hydroxy-2-methylenealkanenitriles (**1**) and 3-hydroxy-2-methylenealkanoates (**2**) with benzene respectively in the presence of a catalytic amount of conc.H_2SO_4.

First we examined the Friedel-Crafts reaction of 3-hydroxy-2-methylene-3-(4-methylphenyl)propanenitrile (**1a**) (0.692g, 4mM) with benzene (5mL) in the presence of a catalytic amount of conc.H_2SO_4 (0.1mL). The best results were obtained when the reaction was carried out at reflux for 30 minutes after the addition of a catalytic amount of H_2SO_4 to the solution of **1a** in benzene at room temperature. Thus the required product [2*Z*]-2-benzyl-3-(4-methylphenyl)prop-2-enenitrile (**3a**) was obtained in 78% yield (0.726g) after usual work up and column chromatography (silica gel, 2% ethyl acetate in hexane). The [*Z*]-stereochemistry was established by comparing the ^{1}H NMR and ^{13}C NMR spectral data[14] with that of the same compound prepared earlier in our laboratory[9].

Scheme 1:

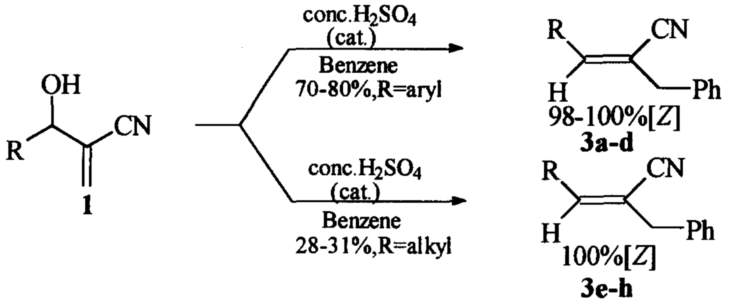

Table 1:The Friedel-Crafts reaction of benzene with 3-hydroxy-2-methylenealkanenitriles[a,b]

substrate	R	Time (minutes)	Product	Yield(%)[c]	(*Z*):(*E*)[d]
1a	4-MeC_6H_4	30	**3a**[14,e]	78	99:1[f]
1b	4-i-$C_3H_7C_6H_4$	30	**3b**[g]	76	100:0
1c	4-ClC_6H_4	30	**3c**[e]	70	100:0
1d	Ph	30	**3d**[e]	80	98:2[f]
1e	n-C_5H_{11}	120	**3e**[h]	28	100:0
1f	n-C_4H_9	120	**3f**[h]	30	100:0
1g	i-C_3H_7	120	**3g**[h]	28	100:0
1h	n-C_3H_7	120	**3h**[e]	31	100:0

a) All reactions were carried out in 4mM scale of alcohol with benzene (5mL) in presence of conc.H_2SO_4 (0.1mL) at reflux temperature. b) Satisfactory spectral data [IR, ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz)] and elemental analyses were obtained for all compounds **3a-3h**. c) Isolated yields of the products after column chromatography (silica gel, 2% ethyl acetate in hexane). d) ^{1}H and ^{13}C NMR indicate the absence of other isomer. e) [*Z*]-Stereochemistry was assigned by comparing the ^{1}H NMR and ^{13}C NMR spectral data with that of the same molecules prepared earlier in our laboratory [9]. f) ^{13}C NMR indicates the presence of very small amounts of the other isomer. g) [*Z*]-Stereochemistry was established by comparing the ^{13}C NMR chemical shift value of the benzylic carbon with that of **3a**. h) [*Z*]-Stereochemistry was established by comparing the ^{13}C NMR chemical shift value of the benzylic carbon with that of **3h**.

We have then extended the same methodology to a variety of 3-hydroxy-2-methylenealkanenitriles to provide the required functionalized trisubstituted olefins in 28-80% yields (Table 1) (Scheme 1). From the Table 1 it is clear that substrates with aryl substituents (R=aryl) provided better yields of the desired Friedel-Crafts products than substrates with alkyl substituents (R=alkyl). However both substrates (R=alkyl,aryl) show [*Z*]-selectivity.

Next we have examined the Baylis-Hillman adducts derived from methyl acrylate *i.e.* methyl 3-hydroxy-2-methylenealkanoates (**2**) as possible stereodefined β-electrophiles for the Friedel-Crafts reaction with benzene, with an objective of studying the stereochemical directive effect of ester group (Scheme 2).

Substrates with aryl substituents (**2a-d**) provided desired Friedel-Crafts products *i.e.* methyl [2*E*]-2-benzyl-3-arylprop-2-enoates(**4a-d**) in high [*E*]-selectivity. However substrates (**2e-2g**) possessing alkyl substituents provided the Friedel-Crafts products (**4e-4g**) as mixtures of *cis* and *trans* isomers (Table 2).

Scheme 2:

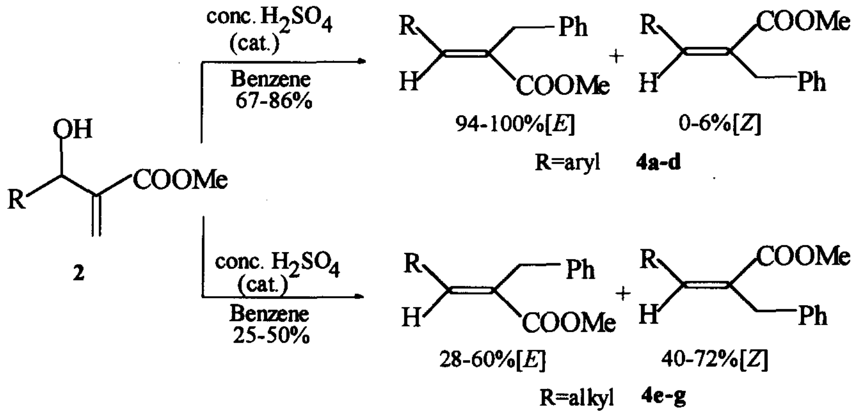

Table 2: The Friedel-Crafts reaction of benzene with 3-hydroxy-2-methylenealkanoates[a,b]

Substrate	R	Time (minutes)	Product	Yield(%)[c]	(*Z*):(*E*)[d]
2a	4-MeC_6H_4	30	**4a**[15]	82	2:98
2b	4-i-$C_3H_7C_6H_4$	30	**4b**	83	0:100
2c	4-ClC_6H_4	30	**4c**	67	6:94
2d	Ph	30	**4d**	86	5:95
2e	i-C_3H_7	90	**4e**	25	72:28
2f	n-C_3H_7	70	**4f**	45	49:51
2g	CH_3	90	**4g**	50	40:60

a) All reactions were carried out in 4 mM scale of alcohol with benzene (5 mL) in presence of conc.H_2SO_4 (0.1 mL) at reflux temperature. b) Satisfactory spectral data [IR, ^1H NMR (200 MHz), and ^{13}C NMR (50 MHz)] and elemental analyses were obtained for all compounds **4a-4g**. c) Isolated yields after column chromatography (silica gel, 2% ethyl acetate in hexane). d) Stereochemical assignments and isomeric purities were based on difference in chemical shifts and integration ratios of isomeric olefinic protons in ^1H NMR analysis.

In summary the H_2SO_4 catalyzed Friedel-Crafts reaction of benzene with the Baylis-Hillman adducts provides a simple and convenient methodology for the synthesis of [2*Z*]-2-benzylalk-2-enenitriles and methyl [2*E*]-2-benzylalk-2-enoates with excellent stereoselectivity, in particular for the molecules possessing aryl substituents.

Acknowledgements: We thank CSIR (New Delhi) for funding this project. MK, RS and SP thank UGC (New Delhi) for providing research fellowships. We also thank COSIST and Special Assistance Programs in Organic Synthesis, in the School of Chemistry, University of Hyderabad.

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14. **Spectral data for 3a**: ^{1}H NMR (200 MHz) (CDCl$_3$): δ 2.35 (s, 3H), 3.66 (s, 2H), 6.91 (s, 1H), 7.17-7.45 (m, 7H), 7.61 (d, 2H, J=8Hz); ^{13}C NMR (50 MHz) (CDCl$_3$): δ 21.13, 41.82, 109.18, 118.67, 126.99, 128.44, 128.59, 129.24, 130.67, 136.53, 140.19, 143.77; (in addition a peak at δ 35.25 with very low intensity (≈1%) corresponding to the minor [*E*] isomer was observed); IR (neat): 2210, 1608 cm^{-1}; MS m/z (%): 233(M$^+$, 100), analysis calculated for $C_{17}H_{15}N$: C, 87.51, H,6.48, N, 6.00; Found C, 87.33, H, 6.51, N, 5.98.
15. **Spectral data for 4a**: ^{1}H NMR (200 MHz) (CDCl$_3$): δ 2.33 (s, 3H); 3.74 (s, 3H), 3.96 (s, 2H), 7.10-7.35 (m, 9H), 7.90 (s, 1H); (in addition peaks at δ 3.58 and 6.60 with very low intensities indicating ≈2% of the [*Z*] isomer were observed); ^{13}C NMR (50 MHz) (CDCl$_3$): δ 21.04, 33.05, 51.70, 125.90, 127.73, 128.09, 128.34, 129.14, 129.65, 132.32, 138.72, 139.32, 140.78, 168.43, (a peak at δ 41.22 with very low intensity corresponding to the minor [*Z*] isomer was also observed); IR (neat): 1712, 1631 cm^{-1}; MS m/z (%): 266(M$^+$, 26.0), analysis calculated for $C_{18}H_{18}O_2$: C, 81.17, H, 6.81, Found C, 81.01, H, 6.80.

(*Received in UK* 18 *December* 1996; *revised* 4 *February* 1997; *accepted* 7 *February* 1997)