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Piperonal as Electrophile in the Baylis-Hillman Reaction. A Synthesis of Hydroxy-β-Piperonyl-γ-Butyrolactone Derivative

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Abstract: Aromatic aldehydes are reluctant to serve as substrates for the Baylis-Hillman reaction at all under the relatively mild conditions. In our research, we have achieved that piperonal could be an useful substrate in this reaction, employing ultrasound technique. The adduct obtained was used in the preparation of key intermediates for the total synthesis of hydroxylated lignans.

The Baylis-Hillman reaction[1] is an emerging carbon-carbon bond forming reaction. It may be broadly defined as a reaction between the α-position of activated alkenes (**I**) and carbon electrophiles containing electron-deficient sp^2 carbon atom (**II**) under the influence of a suitable catalyst, particularly a tertiary amine, producing multifunctional molecules **III** (scheme 1).

Scheme 1

R and/or R' = H, alkyl, aryl
EWG = CO_2R, CN, COR

This reaction has been drawing increased attention, as evidenced by the number of publications describing various aspects of the reaction including its chemo, regio, diastereo and enantioselectivity.[2] As a part of a program aiming at the synthesis of lignans[3] we have envisaged the α-methylene-β-hydroxy ester **1**, as an useful intermediate for those compounds (scheme 2). The Baylis-Hillman adduct bears three functional groups (i.e, hydroxyl, olefin and ester) and may therefore be expected to undergo a variety of organic

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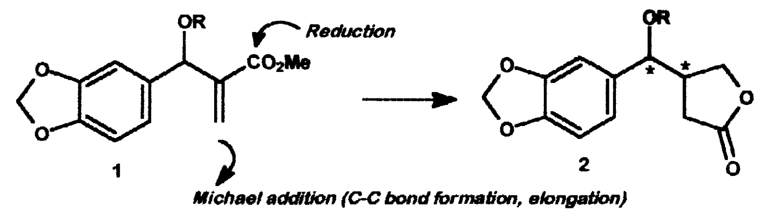
transformations involving regio and stereochemical control. For example, Michael addition employing nucleophilic carbon, followed by ester carbonyl group reduction could provide the basic skeleton of the hydroxylated β-piperonyl-γ-butyrolactone **2**.

Scheme 2



In this way we envisaged piperonal **3** as an appropriate starting material to our synthesis. First attempts to obtain **1** *via* Baylis-Hillman reaction involving piperonal **3**, methyl acrylate **4** and DABCO as catalyst failed (entry 1→3, table 1).[4] These results were previously observed in the literature[5] for aromatic aldehydes bearing electron-releasing groups on the aromatic ring: reaction times of two weeks or more were common and some conditions took more than twenty days to completion.

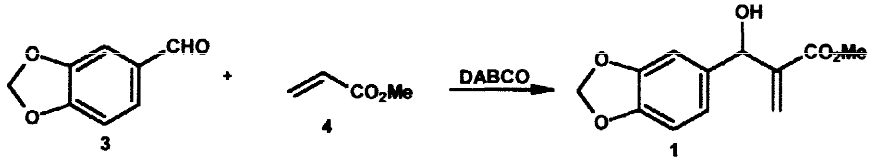


Table 1

entry	conditions[a]	time (days)[b]	yield %[c]
1	A	21	25
2	B	20	30
3	C	15	15 (22)
4	D	8	40 (73)

a:Conditions. A: room temperature, no solvent; B: room temperature, MeOH, THF or dioxane as solvent; C: heat or 0 °C, with or without solvent; D: ultrasound, MeOH, THF or dioxane; b: Time after which the reaction mixture no longer evolved; c:isolated yield based on aldehyde, after purification by column chromatography. In parenthesis, isolated yield based on recovered piperonal.

From table 1 it is clear that ultrasound technique provided better yields of the required product. These results were completely independent of DABCO concentration (10 mol% → 1 mol). Ultrasound technique was also employed in experiments with *p*-chlorobenzaldehyde and *p*-anisaldehyde using condition D. The results are shown in Table 2.

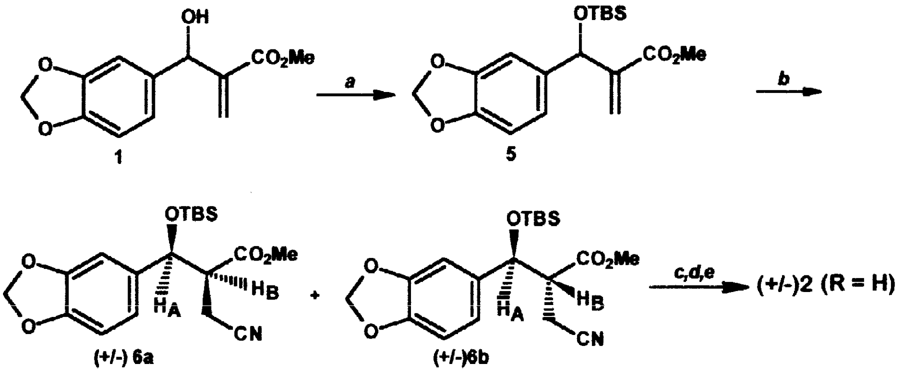
Table 2

entry	substrate	time (days)[a]	yield %[b]
1	*p*-chloro benzaldehyde	4	74(87)
2	*p*-anisaldehyde	4	25(90)

a:Time after which the reaction mixture no longer evolved; b:isolated yield based on aldehyde, after purification by column chromatography. In parenthesis, isolated yield based on recovered aldehyde.

The Baylis-Hillman adduct obtained from piperonal was converted into the *O-t*-butyldimethylsilyl derivative **5** (scheme 3). Michael addition of KCN to **5** in presence of NH_4Cl,[6] provided **6a/6b** (3:1 ratio by ^1H-NMR) in 77% yield after purification. We have not been able to separate **6a/6b** at this stage. The relative stereochemistry of the major diastereoisomer was determined by using ^1H- NMR spectroscopy. Silyl group was removed and the resulting alcohol[7] analysed: the vicinal constant coupling J_{AB} for the major isomer is 5.1Hz, suggesting the correspondent *syn* isomer (**6a**).[8] There is in the literature[9] another example of this *syn* stereoselectivity for the Michael adduct derived from the α-methylene-β-alcoxy-ester.

Scheme 3

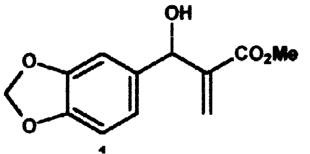
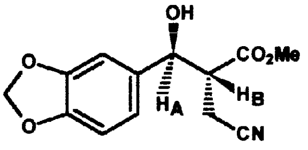
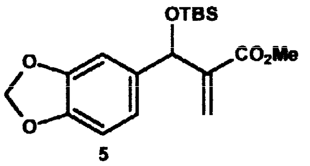
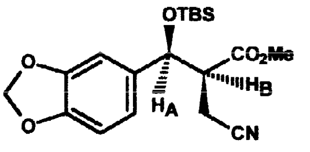


***Reagents and Conditions**: a)TBDMSCl, imidazol, DMF (77%); b)KCN, NH_4Cl, DMF-H_2O (77%); c)$LiBH_4$, THF, 0°C → room temperature, 48h, 79 %; d)Column Chromatography: Hexane/EtOAc, 2:1; e) NaOH 40%, THF-H_2O (3:1), then HCl (52%).*

Ester reduction with $LiBH_4$ gave the intermediate alcohols as a diastereomeric mixture, which were separated by chromatography. Pure alcohol was then converted to **2**, by hydrolysis of the cyano group and cyclisation.

This methodology seems to be versatile since the *anti* diastereoisomer could be obtained as major product when the adduct **1** was directly submitted to the Michael addition of KCN (table 3).

Table 3

Michael Acceptor	Major Adduct	Ratio	Yield (%)
 **1**	 **(+/-)-7**	4:1(anti/syn)	80
 **5**	 **(+/-) 6a**	3:1 (syn/anti)	77

An asymmetric version of this synthetic route can potentially be developed using homochiral alcohol **1**. In this regard it should be noticed that Baylis-Hillman adducts derived from benzaldehyde have been obtained from activated alkenes in optically active form,[2b] or by resolution *via* diastereomer crystallization using a chiral amine-diol as agent.[10] One of these protocols should be provide enantiomerically pure alcohol **1**. Studies on this subject are ongoing.

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References and Notes

1 - For reviews, see, Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001, and Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653.

2 - a) Trost, B. M. *Science* **1983**, *219*, 245. b) For examples of asymmetric Baylis-Hillman reaction, see: Leahy, J. W.; Rafel, S.; Brzezinski, L. J. *J. Am. Chem. Soc.* **1997**, *119*, 4317; Markó, I. E.; Giles, P. R.; Hindley, N. J. *Tetrahedron* **1997**, *53*, 1015; Gilbert, A.; Heritage, T. W.; Isaacs, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 969, and references therein.

3 - For a recent review on lignans, neolignans and related compounds see Ward, R. S. *Nat. Prod. Rep.* **1997**, 43.

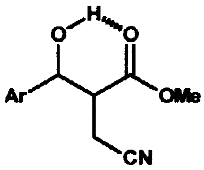
4 - Scale: 0.5 → 3g of aldehyde.

General procedure: A mixture of aldehyde (5mmol), methyl acrilate (6.5 mmol) and DABCO (0.65 mmol) in 2 mL of methanol was sonicated (ultrasonic cleaner, 81W, 40KHz). After completion (see tables), the reaction mixture was diluted with CH$_2$Cl$_2$, washed with brine, and the solvents evaporated *in vacuo*. The residue was dried over Na$_2$SO$_4$ and then purified by column chromatography (silica gel 70-230 mesh, eluated with Hexane-ethyl acetate 80:20) to furnish the Baylis-Hillman adduct.

5 - Forty, Y.; Berthe, M. C.; Caubere, P. *Tetrahedron* **1992**, *48*, 6371.

6 - White, J. D.; Kuo, S.-C.; Vedananda, T. R. *Tetrahedron Lett.* **1987**, *28*, 3061.

7 - This protocol allows an intramolecular hydrogen bonding for both diastereoisomers



8 - Vicinal coupling J$_{AB}$ for the minor isomer is 7.8Hz, suggesting *anti* configuration. Heathcock, C. H., in *Asymmetric Synthesis*, Morrison, J. D., Ed., Academic Press, London, **1984**, *3*, Part B, 115.

9 - Perlmutter, P.; Tabone, M. *Tetrahedron Lett.* **1988**, *29*, 949

10 - Drewes, S.E.; Emslie, N. D.; Field, J. S.; Kahn, A. A; Ramesar, N. *Tetrahedron: Asymmetry* **1992**, *3*, 255.