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Tetrahedron 62 (2006) 954–959

Tetrahedron

Baylis–Hillman adducts between pyridine carboxaldehyde derivatives and cyclic enones☆

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Received 26 July 2005; revised 28 September 2005; accepted 13 October 2005

Abstract—Baylis–Hillman (BH) adducts were synthesized using pyridinecarboxaldehyde derivatives and cyclic enones. The Baylis–Hillman reaction was examined by employing various organic tertiary bases and solvents. It was observed that DBU in MeOH as well as imidazole and *N*-methylimidazole in aqueous MeOH are very effective. These pyridinecarboxaldehydes were reactive and efficient towards the Baylis–Hillman reaction and the resulting adducts are highly stable. The crystal structure for one of the BH adducts was determined.

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1. Introduction

The Baylis–Hillman (BH) reaction is one that results in the formation of a carbon–carbon bond between the α-position of an activated alkene and carbon electrophile containing an electron-deficient sp^2 carbon atom under the influence of a suitable catalyst. The Baylis–Hillman (BH) and related processes have become increasingly important for synthetic organic chemists because the resulting adducts are packed with functional groups and stereochemistry, which can be subjected to numerous transformations.[1] Cyclic enones are also activated alkenes but the Baylis–Hillman reaction of 2-cyclopenten-1-one or 2-cyclohexen-1-one is sluggish or does not occur at all under traditional conditions.[2] To make the reaction more efficient, a variety of methods including physical as well as chemical attempts have been explored. Recently, various organic bases and methods for the synthesis of the Baylis–Hillman adducts of cyclic enones have been developed. Methoxide anion in MeOH solvent,[3] imidazole in aqueous media,[4] azoles in basic water solution,[5] imidazole in basic water solution,[6] the combination of 2,6-diphenyl-4*H*-chalcogeno-4-ones and $TiCl_4$ in methylene chloride,[7] the combination of $LiClO_4$ and DABCO in ether,[8] the use of Et_2AlI in CH_2Cl_2,[9] tributylphosphine combined with 1,1-bi-naphthol,[10] Lewis base effects including DMAP, tributylphosphines and DBU,[11] $TiCl_4$ (Lewis acid) without the use of Lewis base have all been applied to highly reactive aldehydes.[12] Lithium phenylselenide (PhSeLi) catalyzed Baylis–Hillman reaction with cyclic enones,[13] DMAP in aqueous THF used as a catalyst for the Baylis–Hillman reaction between aldehydes (aromatic and aliphatic) and cyclic enones[14] have also been reported. The Baylis–Hillman reactions involving cyclic enones and heterocyclic compounds are less explored. Only Kim et al. reported with quinolinecarboxaldehyde[14b] and Batra et al. reported using 5-isoxazolecarboxaldehyde.[15] To the best of our knowledge there are no other BH reactions involving heterocyclic compounds and cyclic enones reported in the literature. The Baylis–Hillman reaction between pyridine carboxaldehyde/furfuraldehyde and cyclic enones are reported to produce unstable BH adducts.[16] In contrast to earlier reports, we have successfully synthesized Baylis–Hillman adducts between pyridinecarboxaldehyde derivatives and cyclic enones under a variety of conditions. Synthesized Baylis–Hillman adducts containing a pyridine moiety are very stable and for one of the BH adducts an X-ray structure was also determined. The formation of these Baylis–Hillman adducts is found to be very fast and with high yields compared to earlier reports. Such Baylis–Hillman adducts have wide applicability in organic synthesis in preparation of quinolines, naphthyridines, and aza pyrazoles.

2. Results and discussions

The Baylis–Hillman (BH) reaction was conducted using various substituted 2-chloro-pyridine-3-carboxaldehydes[17]

☆ IICT communication no. 050919.

Keywords: Baylis–Hillman reaction; Substituted 2-chloropyridine-3-carboxaldehydes; Cyclic enones; Organic tertiary bases; Solvents; Baylis–Hillman adducts; X-ray crystal structure.

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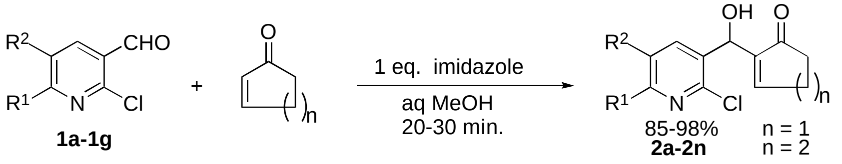
doi:10.1016/j.tet.2005.10.032

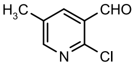
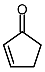
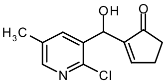
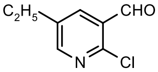
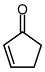
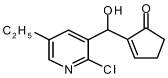
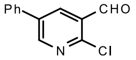
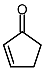
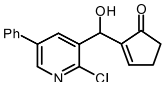
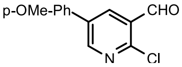
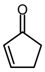
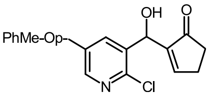
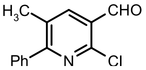
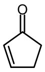
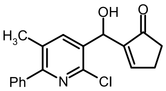
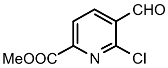
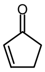
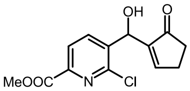
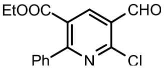
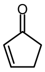
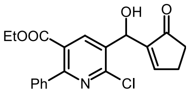
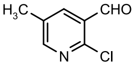
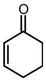
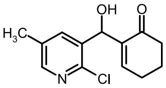
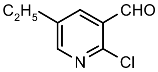
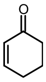
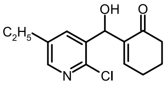
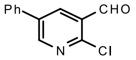
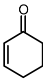
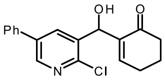
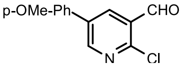
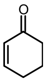
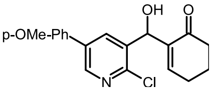
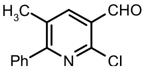
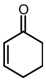
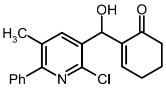
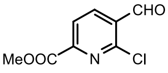
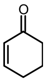
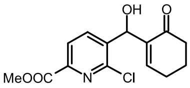
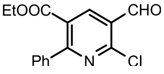
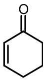
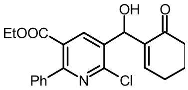


1a: R^1 = H, R^2 = CH_3
1b: R^1 = H, R^2 = C_2H_5
1c: R^1 = H, R^2 = Ph
1d: R^1 = H, R^2 = 4-OMe-C_6H_4
1e: R^1 = Ph, R^2 = CH_3
1f: R^1 = COOMe, R^2 = H
1g: R^1 = Ph, R^2 = COOEt

2a: R^1 = H, R^2 = CH_3, n = 1; **2h:** n = 2
2b: R^1 = H, R^2 = C_2H_5, n = 1; **2i:** n = 2
2c: R^1 = H, R^2 = Ph, n = 1; **2j:** n = 2
2d: R^1 = H, R^2 = 4-OMe-C_6H_4, n = 1; **2k:** n = 2
2e: R^1 = Ph, R^2 = CH_3, n = 1; **2l:** n = 2
2f: R^1 = COOMe, R^2 = H, n = 1; **2m:** n = 2
2g: R^1 = Ph, R^2 = COOEt, n = 1; **2n:** n = 2

Scheme 1.

Table 1. The Baylis–Hillman reaction between substituted pyridinecarboxaldehyde (**1a**–**1g**) and cyclic enones in the presence of imidazole[a,b]

Entry	Aldehyde (**1a**–**1g**)	Cyclic enone	Product (**2a**–**2n**)	Time (min)	Yield (%)[c]
1				20	98
2				20	98
3				25	96
4				20	90
5				25	90
6				15	85
7				20	82
8				25	90
9				25	92
10				30	96
11				25	95
12				30	92
13				22	80
14				25	78

[a] The reactions were conducted in MeOH–H_2O, (1/1, v/v) system at room temperature and the reaction was monitored by TLC.
[b] Mole ratio of aldehyde/cycloalkenone/imidazole = 1:1.2:1.
[c] Isolated yields.