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Ultrasound-promoted access to Baylis–Hillman amines

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ABSTRACT

It is surveyed that the amination of the Baylis–Hillman acetates with primary amines can be dramatically promoted in improved yields and shortened reaction time under ultrasound irradiation than those under conventional stirring. The extensive scope of both amines and acetates are screened to investigate the relationship between substituents and their performance in such transformation.

1. Introduction

The Baylis–Hillman adducts are highly functionalized product of Baylis–Hillman reaction, which is one of the most distinguished and atom-economic C–C bond forming reactions [1–6]. Their amines derivatives are extensively utilized as the effective bricks to construct various significant *N*-atom heterocycles such as pyridines [7,8], quinolines [9,10], pyrimidines [11], pyrroles [12,13], benzodiazepineone [14,15] and so on, which are all molecules with a wide range of bioactivities and pharmaceutical effects. In literature, there are many reports on the synthesis of Baylis–Hillman amines, they can be classified into the following types: (i) nucleophilic substitution of Baylis–Hillman acetates with amines [16–19]; (ii) $Pd(PPh_3)_4$-catalyzed coupling of Baylis–Hillman acetates with amines [20]; (iii) direct amination Baylis–Hillman alcohols with amines [21]. In spite of their potential utility, these methods still suffer from some drawbacks such as difficult handling, prolonged reaction time, unsatisfactory yields, expensive catalyst and limited scope of substrates.

In recent years, ultrasound irradiation is extensively applied in organic reactions due to its special sonochemical effect [22–27]. As we know that the temperature of hot spots caused by the collapse of acoustic caves is generally as high as more than several hundred degrees, this energy can be transferred to the organic molecules and absorbed by them to dramatically raise their intrinsic energy. Due to the thermal effect of ultrasound wave, therefore, much larger amount of molecules can meet the demand for the active energy in a given reaction, leading to the apparent improvement of the reaction efficiency with increased rates and reduced reaction time. In some cases, the thermal effect resulted from the classical heating and ultrasound irradiation will lead to entirely different chemical outcomes. Generally, sonication enhances reaction yields without using harsh conditions. It is also observed that reactions under ultrasound irradiation are commonly easier to work-up than those in conventional stirring methods.

In connection with our interests in the ultrasonic effect on organic reactions [28,29], herein we describe our example for the observably accelerated amination of the Baylis–Hillman acetates in improved yields under ultrasound irradiation. The extended scope of both amines and acetates are sufficient for our research to investigate the relationship between substituents and their performance in such transformation.

2. Methods

2.1. Apparatus and analysis

All the compounds used are analytical reagents and some chemicals are further purified by recrystallization or distillation. Melting points are measured on an X_4 micro-melting point apparatus with the corrected thermometer. The ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra are obtained on a Bruker Avance II DMX400 instrument using $CDCl_3$ as the solvent and Me_4Si as the internal standard. FT-IR spectra are performed as liquid films or KBr pellets on a Nicolet Avatar spectrophotometer. Ultrasound irradiation is performed in a KQ250E ultrasound cleaner, whose frequency is 40 KHz and output power is 250 W. The temperature of the water bath is controlled by addition or removal of water.

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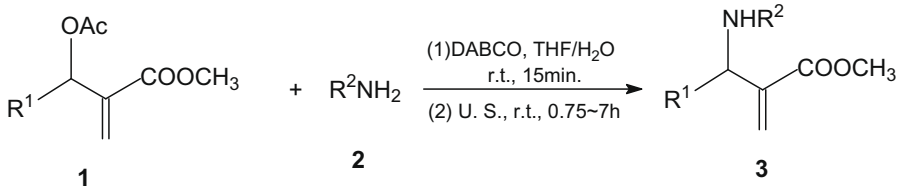
2.2. General procedure for amination of Baylis–Hillman acetates

At room temperature, DABCO (1.5 mmol) is added to the solution of the Baylis–Hillman acetate **1** (1.0 mmol) in THF/H_2O (1:1) (5 mL). The resulted mixture is stirred for 15 min and then the corresponding amine (1.2 mmol) is added. The solution is irradiated at 25–30 °C for the appropriate time (indicated by TLC). When the reaction is over, water is poured to the solution and EtOAc (2×10 mL) is used to extract the mixture. The combined organic layers are washed by brine and dried over anhydrous Na_2SO_4 and the solvent is removed on a rotating evaporator. The residue is purified on a silica column chromatography with petroleum ether/ethyl acetate (5:1) as the eluent to give the corresponding Baylis–Hillman amine as oil or solid [30].

3. Results and discussion

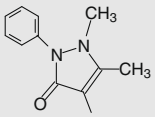
Since there is a successive S_{N2}–S_{N2} nucleophilic substitution in the process of introducing the amino groups at the secondary position of the Baylis–Hillman acetate, an additional base like DABCO should be generally used. The amination of the Baylis–Hillman acetates are carried out at room temperature under either classical stirring or ultrasound irradiation (Scheme 1) to investigate the sonochemical effect on this transformation, and the results of the reaction in the two different methods are listed in Table 1.

It is indicated by Table 1 that there is an obvious sonochemical effect in the amination of the Baylis–Hillman acetates under the ultrasound irradiation. Compared with each case under conventional stirring, ultrasonic amination leads to the dramatically shortened reaction time and the remarkably increased yields. More importantly, the thermal effect of the acoustic cavitations accelerates the amination without the simultaneous promotion of side reactions. However, when the classical stirring is executed in refluxing solvent, the yields of the target molecules have to be remarkably lowered due to the generation of many byproducts and troublesome isolation operation caused by those undesired compounds. This phenomenon is similar to Lee's case [17] in which side products were noticeably increased as the temperature in the amination of Baylis–Hillman acetate with 2-bromoaniline was raised. Apparently, the thermal effects of the conventional heating and the ultrasound irradiation lead to the quite different chemical outcomes. It is assume that there may be some reversible equilibrium between the substrates and the side products, and the reversal transformations from the side products are preferable to occur at much high temperature. In refluxing solvent, while the elevated temperature is so limited that the reversal reactions can not be induced on full scale, the conversion from the substrates to the side products is promoted as the temperature is enhanced. Hence, the observably increased side products are detected in the stirred reaction when it is carried out under heating. However, the super-high temperature resulted from acoustic cavitations is much beneficial to drive the reversal transformations, the relative rate of the conversion to side products is largely decelerated. The side products are turned back into the substrates which further undergo the ami-



Scheme 1.

Table 1
Amination of Baylis–Hillman acetates under ultrasound irradiation and conventional stirring.

Entry	R^1	R^2	Product	Classical reaction[a]		Ultrasound reaction[a]	
				Time (h)	Yield (%)[b]	Time (h)	Yield (%)[b]
1	C_6H_5	C_6H_5	**3a**	8	67	3	84
2	C_6H_5	4-$CH_3OC_6H_4$	**3b**	3	83	1	93
3	C_6H_5	4-$CH_3C_6H_4$	**3c**	5	80	1.5	88
4	C_6H_5	2-$CH_3C_6H_4$	**3d**	8	41	4.5	55
5	C_6H_5	4-ClC_6H_4	**3e**	12	55	5	63
6	C_6H_5	2,5-$(CH_3)_2C_6H_3$	**3f**	12	23	5	41
7	C_6H_5	$C_6H_5CH_2$	**3g**	3	74	1	92
8	C_6H_5	$(CH_3)_2CH$	**3h**	3	70	1	84
9	2-Pyridiyl	C_6H_5	**3i**	10	54	3.5	85
10	4-ClC_6H_4	C_6H_5	**3j**	10	66	3	87
11	2-ClC_6H_4	C_6H_5	**3k**	12	49	5	72
12	4-FC_6H_4	C_6H_5	**3l**	10	56	4	78
13	4-$F_3CC_6H_4$	C_6H_5	**3m**	10	63	4	81
14	4-BrC_6H_4	2-$H_2NC_6H_4$	**3n**	12	32	5	53
15	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	**3o**	4	77	1	88
16	2,4-$Cl_2C_6H_3$		**3p**	6	72	2.5	84
17	2,4-$Cl_2C_6H_3$	3-ClC_6H_4	**3q**	12	31	7	55
18	2,4-$Cl_2C_6H_3$	2-Naphthyl	**3r**	12	25	5	33
19	4-ClC_6H_4	4-HOC_6H_4	**3s**	3	88	0.75	95
20	4-ClC_6H_4	4-$CH_3C_6H_4$	**3t**	5	75	2	91

[a] All reactions are carried out at room temperature.
[b] Isolated yields.