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One-pot facile conversion of the acetates of Baylis–Hillman adducts into substituted fused pyrimidones in aqueous media†

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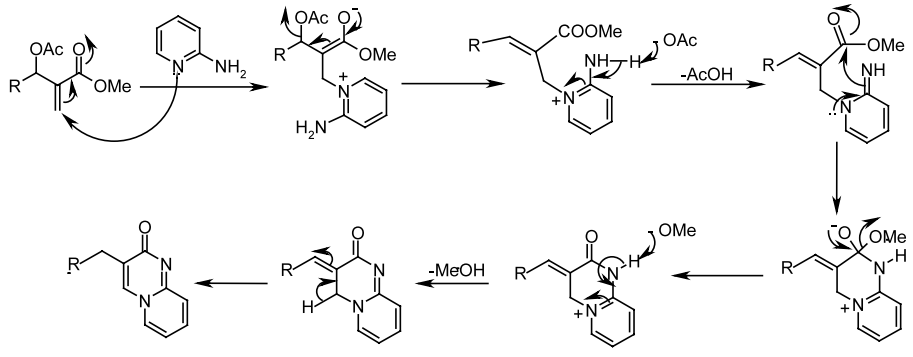
Abstract—A facile, one-pot convenient transformation of the acetates of Baylis–Hillman adducts into fused pyrimidones, i.e. 3-substituted-1,5-diazabicyclo(4.4.0)deca-2,5,7,9-tetraen-4-ones via reaction with 2-aminopyridine in environmentally friendly aqueous media is described. © 2002 Published by Elsevier Science Ltd.

The pyrimidine framework is an important structural moiety present in various biologically active molecules including DNA and RNA.[1–6] In recent years, there has been increasing interest in fused pyrimidine molecules because of their useful and important physiological properties[7–12] and therefore development of simple and convenient methodologies for the synthesis of such molecules represents an attractive and interesting area of research in synthetic organic and medicinal chemistry.[7–10,12–20] We herein describe a one-pot facile synthesis of substituted fused pyrimidine derivatives via the treatment of the acetates of Baylis–Hillman adducts with 2-aminopyridine in environmentally friendly aqueous media.

In recent years, the Baylis–Hillman reaction has become a powerful tool for construction of carbon–carbon bonds in organic chemistry because it is completely atom economical and provides densely functionalized structural units, which have been successfully employed in a variety of interesting organic transformations.[21–33] In continuation of our interest in the development of Baylis–Hillman chemistry as a useful source for important organic transformation methodologies,[28–33] we have undertaken a research program on the application of the acetates of Baylis–Hillman adducts for the synthesis of substituted fused pyrimidine derivatives in aqueous media. A careful literature survey revealed that Lappin[17] reported a reaction of 2-aminopyridine with alkyl acrylates leading to the formation of products via the Michael attack of ring nitrogen onto the acrylate [1,5-diazabicyclo(4.4.0)deca-5,7,9-trien-4-one] and also via the Michael attack of an amino (NH_2) group onto the acrylate [*N*-(pyridin-2-yl)-β-alanine]. Subsequently, Lappin[18] also reported similar results in the reaction of 2-aminopyridine with methyl



Scheme 1.

Keywords: Baylis–Hillman chemistry; fused pyrimidones; environmentally friendly; aqueous media.

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† This paper is dedicated to Professor Herbert C. Brown, an outstanding organic chemist, on the occasion of his 90th birthday.

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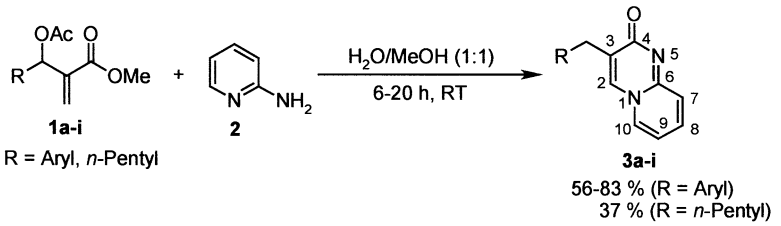

(1)

Table 1. Synthesis of substituted fused pyrimidones (**3a–i**)[34,a]

Acetates	R	Time (h)	Product[b,c]	Yield[d] (%)	Mp (°C)
1a	Phenyl	6	**3a**[e]	77	218–220 (dec.)
1b	*p*-Methylphenyl	6	**3b**[e]	74	230–233 (dec.)
1c	*p*-Ethylphenyl	6	**3c**	83	210–212
1d	*p*-Isopropylphenyl	6	**3d**	75	214–216 (dec.)
1e	*o*-Chlorophenyl	6	**3e**	79	186–188 (dec.)
1f	*p*-Chlorophenyl	6	**3f**	74	212–214 (dec.)
1g	*m*-Methoxyphenyl	6	**3g**	58	207–208
1h	*p*-Methoxyphenyl	6	**3h**	56	219–222 (dec.)
1i	*n*-Pentyl	20	**3i**[e,f]	37	100

[a] All the reactions were carried out on 1 mM scale of the acetates of Baylis–Hillman adducts **1a–i** with 1 mM of 2-aminopyridine **2** in H_2O/MeOH (1:1, 10 mL) at room temperature.

[b] All the fused pyrimidones **3a–i** were obtained as colorless solids and gave satisfactory IR (KBr), ^1H (200 MHz), ^{13}C (50 MHz) NMR spectral data and elemental analyses.

[c] ^1H NMR spectra of the crude products indicated the presence of $\approx$2–5% starting materials in the case of **3a–h**.

[d] Yields of the pure fused pyrimidones obtained after column chromatography (silica gel, 15% MeOH in EtOAc) followed by crystallization (EtOAc).

[e] These compounds were also characterized by mass spectral data.

[f] The ^1H NMR spectrum of the crude product indicated the presence of $\approx$25% of starting material. We have also isolated an unidentified more polar compound in $\approx$20% yield.

propiolate. It occurred to us that the reaction of 2-aminopyridine with the acetates of Baylis–Hillman adducts would provide the desired substituted fused pyrimidine derivatives in a one-pot operation. In this direction we first carried out the reaction of methyl 3-acetoxy-2-methylene-3-phenylpropanoate **1a** with 2-aminopyridine **2** under various conditions. The best results were obtained when the allyl acetate **1a** was treated with 2-aminopyridine **2** in H_2O/MeOH (1:1) at room temperature for 6 h. After the usual work-up and column chromatography followed by crystallization, the desired fused pyrimidone i.e. 3-benzyl-1,5-diazabicyclo(4.4.0)deca-2,5,7,9-tetraen-4-one **3a** was obtained in 77% yield (Eq. (1)).[34,35] Encouraged by this result, we have successfully transformed a representative set of acetates (methyl 3-acetoxy-2-methylene-3-arylpropanoates **1b–h** and methyl 3-acetoxy-2-methyleneoctanoate **1i**) of the Baylis–Hillman adducts into substituted fused pyrimidones **3b–i** via treatment with 2-aminopyridine in aqueous media (Scheme 1 and Table 1). A plausible mechanism for the formation of 3-substituted-1,5-diazabicyclo-(4.4.0)deca-2,5,7,9-tetraen-4-ones is shown in Scheme 1.

In conclusion, we have developed a simple and facile synthesis of fused pyrimidones using the acetates of Baylis–Hillman adducts in environmentally friendly aqueous media, thus demonstrating the application of the Baylis–Hillman chemistry in synthetic organic chemistry.

Acknowledgements

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34. Actually we considered the possibility of the formation of two products, i.e. **3** and **4**. Molecules with similar skeletons to **4** are known in the literature (for example **A**, **B**, **C**, **D**).[12–14] It is observed in the ^{1}H NMR spectra (in $CDCl_3$ or DMSO-d_6) that the signal for H-10 proton of compounds **A**, **B**, **C**, **D** appears at $\approx\delta$ 8.96–9.22 (see below). In the ^{1}H NMR spectra (28.5% CD_3OD in $CDCl_3$) of our molecules, **3a**–**i**, the H-10 proton appears as a doublet at $\approx\delta$ 7.73–7.91 and no peak was observed at $\approx\delta$ 8.00–9.30. [Also in the ^{1}H NMR spectra (in $CDCl_3$) of the crude products (**3a**–**h**) no peak was observed at $\approx\delta$ 8.00–9.30. However, in the case of **3i**, the ^{1}H NMR spectrum (in $CDCl_3$) of the crude product showed some peaks at δ 8.00–8.30. In fact, we have also isolated an unidentified more polar compound in $\approx$20% yield and in its ^{1}H NMR spectrum (in $CDCl_3$) no peak was observed at $\approx\delta$ 8.50–9.30]. To confirm the structures, we have also recorded the ^{1}H NMR spectrum of **3a** (R = phenyl) in DMSO-d_6 and it was noticed that the H-10 proton appeared as a doublet at δ 8.17 and no peak was observed at $\approx\delta$ 8.30–9.30. Therefore, we have assigned the structure **3** for all these fused pyrimidones. It is also worth mentioning here that the H-10 proton in the compound **E** (in $CDCl_3$–DMSO-d_6) appears at δ 8.13 (Ref. 15). Our assignment is in close agreement with that of **E**.
35. **Spectral data for 3a**: mp = 218–220°C (dec.); IR (KBr) 1649, 1602 cm^{-1}; ^{1}H NMR (200 MHz) (28.5% CD_3OD in $CDCl_3$) 3.91 (s, 2H), 6.90–7.02 (m, 1H), 7.22–7.76 (m, 8H), 7.85 (d, 1H, J = 6.8 Hz); ^{13}C NMR (50 MHz) (28.5% CD_3OD in $CDCl_3$) 34.02, 113.53, 123.52, 126.73, 128.68, 129.24, 130.18, 132.72, 135.76, 135.85, 137.13, 151.02, 168.57; MS (m/z) 236 (M^+). Anal. calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.18; H, 5.10; N, 11.91.