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# Simple, facile and one-pot conversion of the Baylis–Hillman acetates into 3,5,6-trisubstituted-2-pyridones

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ABSTRACT

A facile route for the synthesis of novel 3,5,6-trisubstituted-2-pyridones from the acetylated Baylis–Hillman esters with β-enamino esters or β-enamino nitriles in one pot with good yields is described.

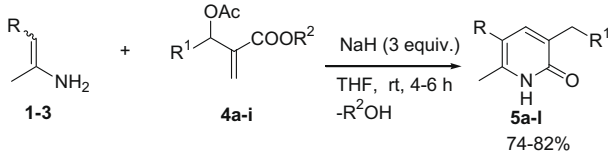


The 2-pyridone core structure is an important heterocyclic framework that has attracted the attention of synthetic organic chemists for many years because these structural motifs are found in a very large number of biologically active natural alkaloids.[1] Natural products with this structure have emerged during the last ten years as a potent antitumor,[2] antifungal,[3] antiviral,[4] psychotherapeutic[5] agents, and as an antibiotic.[6] Moreover 2-pyridone derivatives are the key intermediates in the synthesis of the corresponding pyridine, quinoline, quinolizidine and indolizidine alkaloids.[7] Amrinone, milrinone and their analogues which have 2-pyridone moiety are used as cardiotonic agents for the treatment of heart failure.[8] Due to their immense biological properties, development of simple and convenient methodologies for the synthesis of substituted 2-pyridone derivatives from easily available starting materials is still in demand.[9] In continuation of our research on the synthesis of heterocyclic compounds and application of the Baylis–Hillman chemistry,[10] herein we report a facile and one-pot synthesis of 3,5,6-trisubstituted-2-pyridones upon treating the acetylated Baylis–Hillman esters with β-enamino esters or β-enamino nitriles (Scheme 1).

In recent years products of the Baylis–Hillman (BH) reaction and the derivatives produced from them have been effectively utilised for the generation of attractive densely functionalised molecules by employing simple alterations.[11] Especially acetates of the BH adducts have been successfully employed in a number of transformations leading to the synthesis of various important and useful heterocyclic molecules and natural products.[11,12] One recent report by Batra and co-workers informs the synthesis of 2-pyridones in two steps from acetylated BH nitriles.[13]

The starting substrates for the study, that is, enamines **1, 2** and acetylated BH esters **4a–i** were synthesised according to the literature procedure[14] and the enamine **3** was obtained commercially. Accordingly, we first examined ethyl-3-aminocrotonate **1** with the acetylated BH ester **4a** as a choice of substrate using various bases under different reaction conditions[15,16] (Table 1). After many trials we finally report an efficient procedure for the synthesis of 2-pyridone **5a** in good yield (82%), when the reaction was carried out in THF as a solvent by using NaH as base at room temperature.

Encouraged by the successful results, we examined other substituted BH acetates with various enamines **1–3** and the results[17] are summarised in Table 2. A plausible mechanism for the formation of 2-pyridone derivative **5a** is shown in Scheme 2. This reaction is interesting because the carbanion generated at α-position of **1** (by the aid of NaH) attacks β-position of external double bond of the acetylated BH ester **4a** via $S_N2'$ mechanism by which C–C bond formation takes place and subsequent migration of the double bond with elimination of the acetate group occurs simulta-




**Scheme 1.** (For 1–3, **4a–i** and **5a–l** see the Table 2).

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**Table 1**
Effect of base on the reaction of BH acetate **4a** (2.2 mmol) with ethyl-3-aminocrotonate **1** (2 mmol)

| Entry | Base[a] (equiv) | Solvent | Time (h) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | $NEt_3$ (3) | EtOH[c] | 24 | 0 |
| 2 | $K_2CO_3$ (3) | $CH_3CN$[c] | 24 | 0 |
| 3 | *t*-BuOK (3) | THF (rt) | 06 | 60 |
| 4 | NaH (1) | THF (rt) | 24 | 12 |
| 5 | NaH (2) | THF (rt) | 08 | 50 |
| 6 | NaH (3) | THF (rt) | 04 | 82 |
| 7 | NaH (3) | THF (reflux) | 04 | 61 |
| 8 | NaH (4) | THF (rt) | 04 | 66 |

[a] The equivalents of the base used with respect to **1**.
[b] Isolated yields after column chromatography.
[c] The reaction was carried out at rt and also under reflux.

neously to give intermediate **I** which was not isolated during the reaction. Thus formed intermediate **I** undergoes intramolecular cyclisation forming C–N bond by reacting with ester moiety to give compound **II**, further in which the double bond migration takes place to give 3,5,6-trisubstituted-2-pyridone **5a** with good yield involving three chemical transformations in one-pot procedure. Thus proposed mechanism explains the requirement of 3 equiv of base NaH (Scheme 2). This method worked well on both BH substrates derived from aliphatic and aromatic aldehydes and not much difference was observed in the yield whether the substrate used was either ethyl 3-aminocrotonate **1** or methyl 3-aminocrotonate **2** or 3-aminocrotononitrile **3**. In all cases, the reactions were clean and afforded the 3,5,6-trisubstituted-2-pyridones **5a–l** in good yields.

**Table 2**
One-pot synthesis of 3,5,6-trisubstituted-2-pyridones from Baylis–Hillman acetates

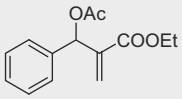
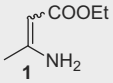
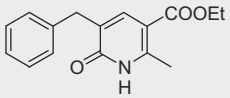
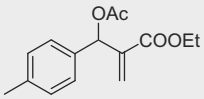
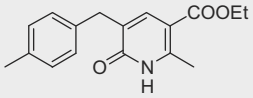
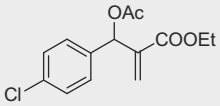
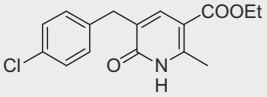
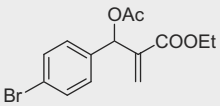
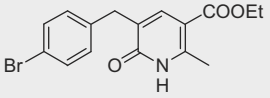
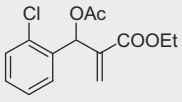
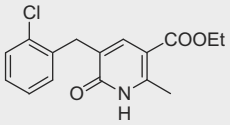
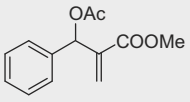
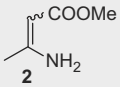
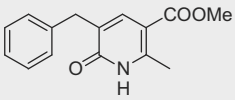
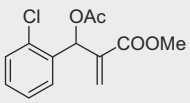
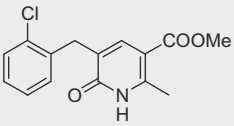
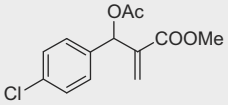
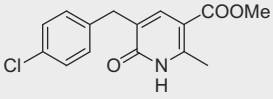
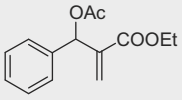
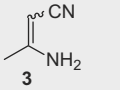
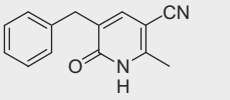
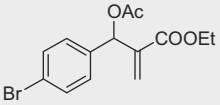
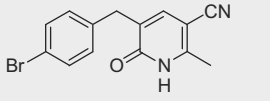
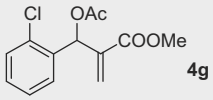
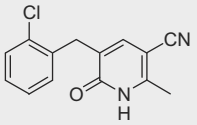
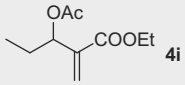
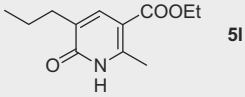
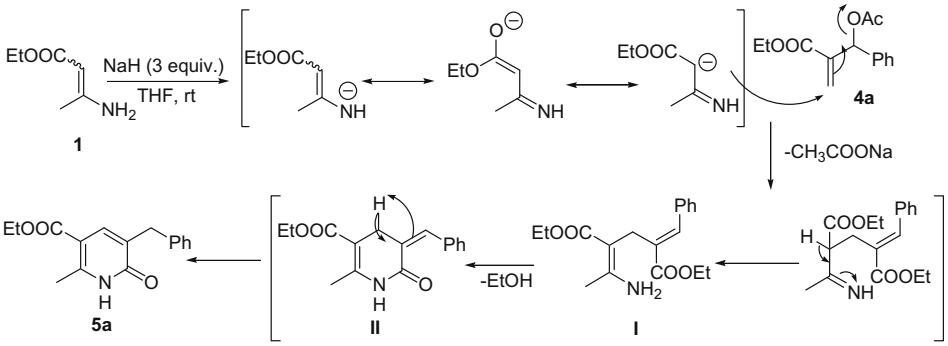
| Entry | BH acetate | Enamine | Product | Yield[a,b] (%) |
|---|---|---|---|---|
| 1 |  **4a** |  **1** |  **5a** | 82 |
| 2 |  **4b** | **1** |  **5b** | 75 |
| 3 |  **4c** | **1** |  **5c** | 78 |
| 4 |  **4d** | **1** |  **5d** | 77 |
| 5 |  **4e** | **1** |  **5e** | 80 |
| 6 |  **4f** |  **2** |  **5f** | 78 |
| 7 |  **4g** | **2** |  **5g** | 74 |
| 8 |  **4h** | **2** |  **5h** | 78 |
| 9 |  **4a** |  **3** |  **5i** | 77 |
| 10 |  **4d** | **3** |  **5j** | 75 |

**Table 2** (*continued*)

| Entry | BH acetate | Enamine | Product | Yield [a,b] (%) |
|---|---|---|---|---|
| 11 |  **4g** | **3** |  **5k** | 76 |
| 12 |  **4i** | **1** |  **5l** | 77 |

[a] All structures were characterised by NMR, IR and mass spectroscopy.
[b] Isolated yields of products after column chromatography.




**Scheme 2.**

During the course of our synthesis, Kim et al. reported the synthesis of tri-substituted 2-pyridone compounds in two steps from the BH acetates.[18] A quick comparison of our work with reported work clearly indicates that the reported method is a two-step reaction, requires 15 h reaction time, higher temperature, excess amount of $NH_4OAc$ (20 equiv) and the product was formed along with side products. Hence the procedure reported herein provides significant advantages in both yield and practicality over recently reported two-step routes to similar 2-pyridones. We believe that this reaction has enough scope for further investigations.

In conclusion, we have prepared a series of 3,5,6-trisubstituted-2-pyridones in very good yields from the acetylated Baylis–Hillman esters in a one-pot procedure.

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15. The rearrangement of the Baylis–Hillman acetate **4a** into corresponding primary acetate was observed while treating it with **1** by $K_2CO_3$ at both rt and refluxing conditions.
16. As per one of the reviewers suggestion, we carried out the reaction between **4a** and **1** by taking mixture of bases NaH (1 equiv) and $K_2CO_3$ (2 equiv) but the yield was similar to entry 4 in Table 1.
17. *General experimental procedure*: To a well-stirred solution of NaH (60% in paraffin oil, 6 mmol) in dry THF (15 mL) was added β-enamino ester or β-enamino nitrile (2 mmol) dissolved in dry THF (5 mL) at rt under nitrogen atmosphere and allowed to stir for 15 min (at the same temperature).Then acetylated Baylis–Hillman ester (2.2 mmol) disolved in THF (5 mL) was added slowly and allowed to stir at rt for 4–6 h. On completion (monitored by TLC) solvent was removed under reduced pressure and the residue was diluted with $H_2O$ (20 mL) and extracted with EtOAc (3×30 mL). The combined organic layers were dried over $Na_2SO_4$, solvent was evaporated in vacuo and purified by silica gel column chromatography using ethyl acetate/hexane (1:4) as eluent to afford pure compounds **5a–l**. For analytical purpose it is further purified by recrystallisation from MeOH. *Spectral data for selected compounds:* Compound **5c**: Yield 78%; white solid, mp 191–194 °C; IR (KBr) 3430, 2970, 2904, 1716, 1652, 1581, 1231, 1080; $^1$H NMR ($CDCl_3$+DMSO-$d_6$, 200 MHz) $\delta$ 11.98 (br s, 1H), 7.63 (s, 1H), 7.20 (br s, 4H), 4.23 (q, $J$ = 7.16 Hz, 2H), 3.70 (s, 2H), 2.54 (s, 3H), 1.32 (t, $J$ = 7.16 Hz, 3H); $^{13}$C NMR (DMSO-$d_6$ 75 MHz) $\delta$ 164.60, 162.47, 151.13, 138.86, 138.23, 130.57, 130.43, 128.10, 127.57, 106.06, 60.08, 34.20, 18.51, 14.11; HRMS (ESI) $m/z$ calcd for $C_{16}H_{17}NO_3$ $[M+H]^+$ 306.0906, found 306.0891. Compound **5f**. Yield 78%; white solid, mp 210–213 °C; IR (KBr) 3415, 2897, 1719, 1653, 1278, 1234, 1195, 1084; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 13.07 (br s, 1H), 7.74 (s, 1H), 7.24–7.14 (m, 5H), 3.80 (s, 3H), 3.79 (s, 2H), 2.64 (s, 3H); $^{13}$C NMR (DMSO-$d_6$ 75 MHz) $\delta$ 165.04, 162.54, 151.07, 139.72, 137.88, 128.66, 128.26, 128.15, 125.99, 105.78, 51.47, 34.76, 18.47; HRMS (ESI) $m/z$ calcd for $C_{15}H_{15}NO_3Na$ $[M+Na]^+$ 280.0941, found 280.0944. Compound **5j**. Yield 75%; white solid, mp 239–242 °C; IR (KBr) 3447, 3020, 2791, 2222, 1642, 1579, 1221; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 13.29 (br s, 1H), 7.43 (d, $J$ = 8.30 Hz, 2H), 7.19 (s, 1H), 7.10 (d, $J$ = 8.30 Hz, 2H), 3.72 (s, 2H), 2.53 (s, 3H); $^{13}$C NMR (DMSO-$d_6$ 50 MHz) $\delta$ 161.75, 153.37, 138.69, 137.44, 131.04, 130.86, 129.19, 119.15, 117.21, 88.20, 34.19, 17.81. HRMS (ESI) $m/z$ calcd for $C_{14}H_{11}N_2ONaBr$ $[M+Na]^+$ 324.9948, found 324.9952. Compound **5l**. Yield 77%; white solid, mp 149–151 °C; IR (KBr) 3296, 3150, 2964, 2877, 1712, 1656, 1580, 1377, 1277, 1230; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 13.17 (br s, 1H), 7.78 (s 1H), 4.30 (q, $J$ = 7.17 Hz, 2H), 2.70 (s, 3H), 2.47 (t, $J$ = 7.36 Hz, 2H), 1.69–1.57 (sext, $J$ = 7.55, 7.36 Hz, 2H), 1.38 (t, $J$ = 7.17 Hz, 3H), 0.98 (t, $J$ = 7.55 Hz, 3H); ESIMS $m/z$ 224 $[M+H]^+$.
18. Kim, S. H.; Lee, S.; Kim, S. H.; Kim, J. N. *Bull. Korean Chem. Soc.* **2008**, *29*, 1815.