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A concise α-amino acid-based synthetic approach to [1,4]oxazepin-2-ones from Baylis–Hillman adducts

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ABSTRACT

An original two-step process for the synthesis of [1,4]oxazepin-2-ones starting from Baylis–Hillman (BH) adducts is reported. The protocol involves a nucleophilic substitution of the acetates of BH adducts with renewable natural α-amino esters followed by base-catalyzed intramolecular Michael addition. These sequential reactions are operationally simple, performed under ambient conditions, and give 81–93% yields of the target [1,4]oxazepin-2-ones. Thus, the present invention opens up a new aspect for the synthetic utility of BH adducts.

In general, the chemistry of seven-membered heterocycles has been far less extensively studied than that of five- and six-membered ones as well as the inherently strained small ring heterocycles. The abundance of oxygen and nitrogen-containing seven-membered and medium rings in natural products, pharmaceuticals, and agrochemicals continues to ensure that they are important synthetic targets for organic chemists.[1] Over the past decades, the design and synthesis of heterocycles having a ring size in the range of 7–11 have received a lot of attention in synthetic organic chemistry as a consequence of their wide variety of applications such as biologically active natural products,[2] drug candidates,[3] materials,[4] and catalysts.[5] Heterocyclic seven-membered rings constitute the core or a key fragment of a number of bioactive compounds including that isolated from natural sources.[6,7] Among them, seven-membered heterocycles with two heteroatoms in 1,4-distance are known to possess manifold biological activities. In particular, aryl-annelated [1,4]oxazepine[8] units are crucial moieties in several psychoactive pharmaceuticals, for example, oxazepam (a tranquilizer).[9] Moreover, Mukaiyama[10] and Tietze[11] have shown that 6-benzylidene-oxazepane-5,7-dione is a valuable chiral template for stereoselective synthesis.

The Baylis–Hillman (BH) reaction is a synthetically useful and atom-economical carbon–carbon bond-forming reaction yielding functionalized allylic alcohols, thereby providing handles for further manipulation in a multitude of synthetic organic transformations.[12] BH adducts incorporate a minimum of three chemospecific groups, that is, hydroxyl (or amino), alkene, and electron-withdrawing groups. These groups could be appropriately tailored to generate an array of cyclic scaffolds directly from the BH adducts. Very recently, an excellent review has covered applications of BH adducts in the synthesis of cyclic frameworks.[13] At present, the adoption of renewable natural sources as starting materials by the chemical industry is necessary and topical, as our mineral resources continue to be consumed at a prodigious pace. Natural α-amino acids and their derivatives provide the most abundant renewable natural chiral pool, and can form efficient, practical, facile precursors for various organic syntheses.[14]

The synthesis of 7- to 11-membered heterocycles is difficult because of enthalpic and entropic reasons, which make direct cyclization methods ineffective unless certain conformational restraints are present in the acyclic precursor.[2a,15] Hence, the development of general and effective protocols to construct 7- to 11-membered heterocyclic systems is an interesting target of investigation. Here, BH chemistry has been applied for this purpose. BH adducts are useful substrates for a variety of nucleophilic reactions such as S_N2, S_N2', and Michael addition, and amino acids/alcohols provide two nucleophilic groups, which pose severe chemoselectivity problems in their combinations. This fact should be the main reason why only a few reports are available in the literature on the reaction of BH adducts with amino acids/alcohols.[16]

In view of the above valid points and our ongoing efforts to develop new convenient cyclization processes,[17] we were intrigued by the question of whether allylic acetates **4** could be reacted with

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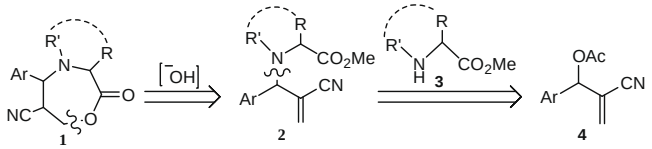
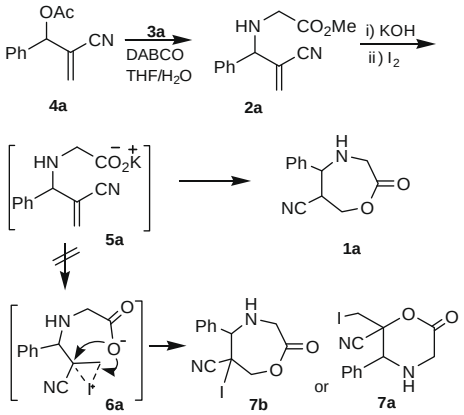


Scheme 1. Disconnection approch to [1,4]oxazepin-2-ones **1**.

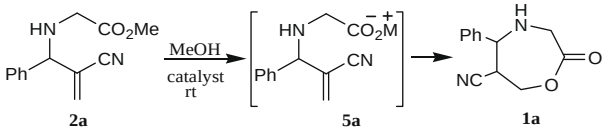


Scheme 2. Formation of [1,4]oxazepin-2-one **1a** from BH adduct **4a**.

esters of α-amino acids **3** and subsequently cyclized under basic conditions to afford [1,4]oxazepin-2-ones **1**, a family of compounds not explored to date (Scheme 1).

Initially, we investigated the possibility of the formation of **7a** or **7b** via iodolactonization as depicted in Scheme 2. Thus, BH adduct **4a** was reacted with glycine ester **3a** in THF/H_2O (1:1) in the presence of DABCO to afford **2a**, which on treatment with KOH and molecular iodine in methanol did not undergo iodolactonization, and [1,4]oxazepin-2-one **1a** was obtained in 84% yield instead of **7a** or **7b**. Interestingly, the same yield (84%) of **1a** was obtained, when the reaction was performed without using molecular iodine. This demonstrates that **5a** is a very good substrate for a facile 7-endo-trigonal ring closure rather than an iodolactonization reaction. The formation of iodonium ion **6a** is probably hampered by the electron-deficient olefinic bond of **5a**; hence, the ensuing iodolactonization to furnish **7a** or **7b** is not feasible (Scheme 2).

Table 1
Optimization of the catalyst for the cyclization of **2a** to afford **1a**[a]



Entry	Catalyst	Time[b] (h)	Yield[c] (%)
1	LiOH	12	51
2	NaOH	6	70
3	KOH	3	84
4	$Ca(OH)_2$	12	42
5	$Ba(OH)_2$	10	48
6	NH_4OH	12	33
7	0.1M TFA/H_2O	48	30
8	0.1M H_2SO_4/H_2O	21	38

[a] For the experimental procedure, see Ref. 18.
[b] Time for completion of the reaction at rt as indicated by TLC.
[c] Yield of isolated and purified products.

Table 2
Base-catalyzed synthesis of [1,4]oxazepin-2-ones **1** at rt (Scheme 3)

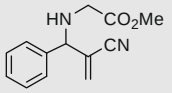
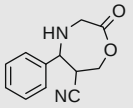
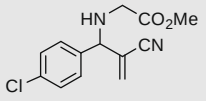
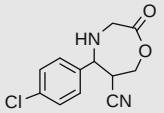
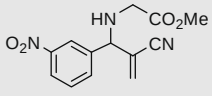
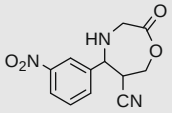
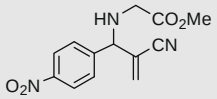
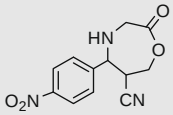
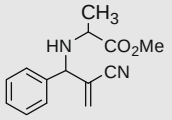
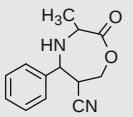
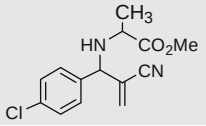
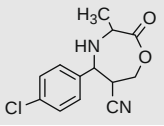
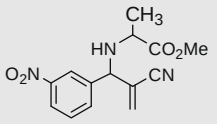
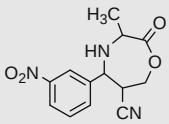
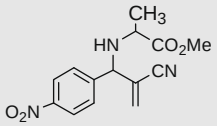
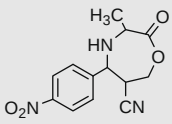
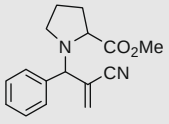
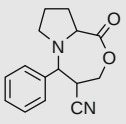
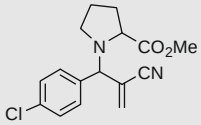
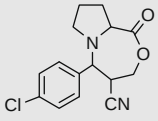
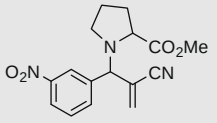
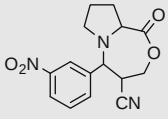
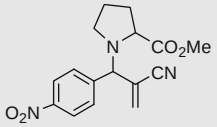
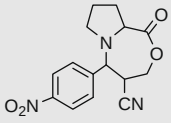
Entry	Ester **2**	Final product **1**	Reaction time[a] (h)	Yield[b,c] (%)
1	 **2a**	 **1a**	3	84
2	 **2b**	 **1b**	2.5	90
3	 **2c**	 **1c**	3	87
4	 **2d**	 **1d**	2	93
5	 **2e**	 **1e**	3.5	85
6	 **2f**	 **1f**	2.5	89

Table 2 (*continued*)

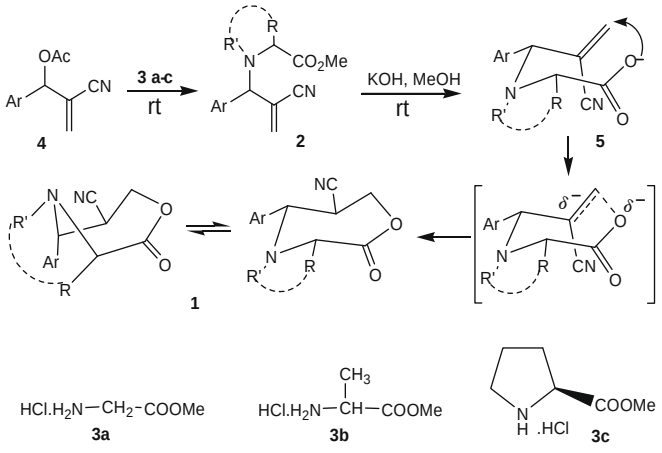
Entry	Ester **2**	Final product **1**	Reaction time[a] (h)	Yield[b,c] (%)
7	 **2g**	 **1g**	3	86
8	 **2h**	 **1h**	2	90
9	 **2i**	 **1i**	4	81
10	 **2j**	 **1j**	3.5	85
11	 **2k**	 **1k**	4	83
12	 **2l**	 **1l**	3	89

[a] Time for completion of the reaction at rt as indicated by TLC.
[b] Yield of isolated and purified products.
[c] All compounds gave C, H and N analyses within ±0.38% and satisfactory spectral (IR, ^{1}H NMR, ^{13}C NMR and EIMS) data.

Next, optimization of the catalyst for the cyclization of **2a** to afford **1a** was investigated and it was found that among the catalysts tested, KOH gave the best result (Table 1, entry 3). It is worth noting that the catalyst used exhibited distinguishing effects as manifested by reaction times and yields (Table 1). In general, bases (Table 1, entries 1–6) were found to be more effective than acid catalysts (Table 1, entries 7 and 8). This is presumably because, in the former case, the nucleophilic carboxylate anion is available for causing the cyclization, whereas in the latter case, a relatively weaker nucleophile –COOH (**5a**, $K^+ = H$) is available (Scheme 2). The divergence in the observed catalytic behaviour of bases (Table 1, entries 1–6) can be explained in terms of their strength, which increases the rate of hydrolysis of the adduct **2a** as well as the ability of their countercations to form an ion-pair with the carboxylate anion, thereby affecting its nucleophilicity. Thus, the highest catalytic efficacy of KOH is attributed to its highest basicity and to the formation of a weak ion-pair between K^+ and $-COO^-$, which leaves the nucleophile $-COO^-$ much more open than in the case of other bases (Table 1, entries 1–6).

The present optimized synthesis of [1,4]oxazepin-2-ones **1** involves stirring of BH adduct-derived α-amino esters **2** with KOH in methanol at rt for 2–4 h to afford **1**.[18] In order to investigate the substrate scope, a wide range of esters **2** incorporating various aryl and α-amino acid moieties were reacted under optimized conditions. As listed in Table 2, all the reactions went well and gave the desired products **1** in consistently good yields (81–93%). The requisite BH adduct-derived α-amino esters **2** and their precursor BH adducts **4** were prepared employing known methods.[16a,19] Carboxylate anions **5** generated by basic hydrolysis of esters **2** have very suitable stereochemical configuration for cyclization through intramolecular Michael addition via a seven-membered transition state. The seven-membered transition state probably exists in chair form and ring closed via 7-endo-trigonal ring closure (Scheme 3).

In summary, we have demonstrated a concise α-amino acid-based synthetic approach to disubstituted [1-4]oxazepin-2-ones via sequential intermolecular nucleophilic substitution and intramolecular Michael addition reactions. The present simple protocol involves the combination of renewable natural α-amino acids and BH chemistry for the synthesis of chemically and pharmacologi-



Scheme 3. A plausible mechanism for the formation of [1,4]oxazepin-2-ones **1**.

cally interesting 1,4-oxazepines, and is capable of being extended to amino acid-derived chiral heterocycles of this family. Thus, the present invention opens up a new aspect for the synthetic utility of BH adducts.

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18. *General procedure for the synthesis of [1,4]oxazepin-2-ones* **1**: A solution of α-amino ester **2** (1 mmol) and KOH (1.5 mmol) in methanol (3 mL) was stirred at rt for 2–4 h (Table 2). After completion of the reaction (monitored by TLC), water (10 mL) was added and the reaction mixture was extracted with ethyl acetate (2 × 10 mL). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting crude product was purified by silica gel column chromatography using a mixture of hexane/ethyl acetate (9:1) to afford an analytically pure sample of **1**. *Physical data of representative compounds*. Compound **1a**: Colorless liquid, yield 84%. IR: ν_{max} (neat) 3300, 2989, 2243, 1740, 1604, 1495, 1451, 752, 705, cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$/TMS): δ 2.13 (s, 1H, NH), 3.20 (d, 1H, J = 11.2 Hz, $COCH_a$), 3.31 (d, 1H, J = 11.2 Hz, $COCH_b$), 3.48–3.56 (m, 2H, CHCN and PhCH), 4.36–4.42 (m, 2H, OCH_2), 7.25–7.71 (m, $5H_{arom}$). ^{13}C NMR (100 MHz; $CDCl_3$/TMS): δ 34.0, 55.5, 60.2, 72.1, 119.2, 124.3, 128.0, 128.8, 139.0, 172.0. EIMS (m/z): 216 (M^+). Anal. Calcd for $C_{12}H_{12}N_2O_2$, C, 66.65; H, 5.59; N, 12.96. Found: C, 66.95; H, 5.36; N, 12.65. Compound **1e**: Colorless liquid, yield 85%. IR: ν_{max} (neat) 3302, 2980, 2850, 2240, 1740, 1603, 1490, 1450, 754, 708 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$/TMS): δ 2.04 (s, 1H, NH), 1.91 (d, 3H, J = 7.5 Hz, $-CH_3$), 3.33 (q, 1H, J = 7.5 Hz, COCH), 3.43–3.54 (m, 2H, CHCN and PhCH), 4.27–4.32 (m, 2H, OCH_2), 7.05–7.71 (m, $5H_{arom}$). ^{13}C NMR (100 MHz; $CDCl_3$/TMS): δ 20.2, 34.2, 57.2, 60.5, 72.1, 119.1, 128.6, 129.1, 132.1, 141.0, 172.6. EIMS (m/z): 230 (M^+). Anal. Calcd for $C_{13}H_{14}N_2O_2$, C, 67.81; H, 6.13; N, 12.17. Found: C, 67.46; H, 6.49; N, 12.54. Compound **1i**: Colorless liquid, yield 81%. IR: ν_{max} (neat) 2950, 2254, 1745, 1600, 1491, 1438, 750, 698 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$/TMS): δ 1.46–1.96 (m, 4H, C–CH_2CH_2–C), 2.20–2.28 (m, 2H, NCH_2), 3.35 (t, 1H, J = 6.80 Hz, COCH), 3.41–3.53 (m, 2H, CHCN and PhCH), 4.30–4.37 (m, 2H, CH2O), 7.05–7.71 (m, $5H_{arom}$). ^{13}C NMR (100 MHz; $CDCl_3$/TMS): δ 23.2, 28.3, 34.2, 55.1, 60.5, 69.2, 72.1, 119.1, 128.6, 129.8, 132.1, 141.0, 172.6. EIMS (m/z): 256 (M^+). Anal. Calcd for $C_{15}H_{16}N_2O_2$, C, 70.29; H, 6.29; N, 10.93. Found: C, 70.67; H, 6.50; N, 11.21.
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