Synthesis of 3-(Arylmethylene)-1,5-benzodiazepin-2-ones from Baylis-Hillman Acetates

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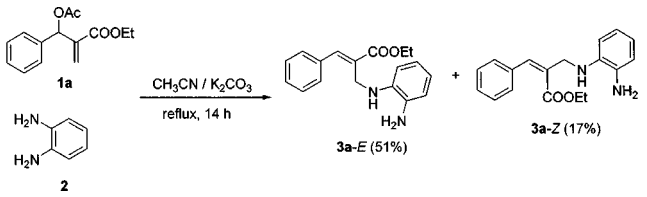
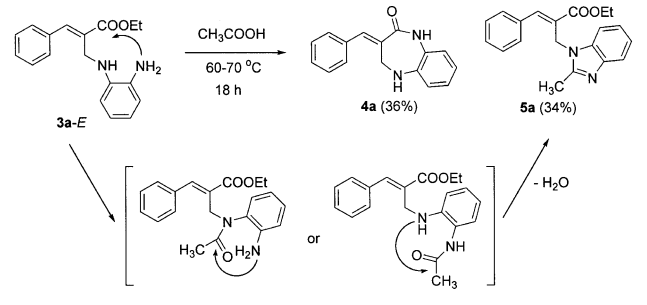
Seven-membered heterocycles with two heteroatoms in a 1,4-relationship are known to possess many biological activities. Particularly, aryl-annelated [1,4]diazepine and [1,4]oxazepine are crucial moieties in many psychoactive pharmaceuticals.[1,2] 6-Benzylidene-oxazepane-5,7-dione is known as a valuable chiral intermediate.[3] Arylmethylene benzodiazepinones have been used for the synthesis of pesticidal pyrazolobenzodiazepines and thiazinobenzodiazepines.[4] Besides of these papers, numerous reports have been reported regarding the synthesis or biological activity of benzodiazepines[1] or dibenzodiazepines.[2] Recently, Reiser *et al*. have reported combinatorial liquid-phase synthesis of [1,4]oxazepin-7-ones *via* the Baylis-Hillman reaction.[5]

In these respects, we intended to prepare some 3-(arylmethylene)-1,5-benzodiazepin-2-one derivatives from the Baylis-Hillman acetates. The reaction of the Baylis-Hillman acetate **1a** and 1,2-phenylenediamine (**2**) in acetonitrile in the presence of potassium carbonate gave the allylic substitution product **3a**[6] (Scheme 1). The *E* and *Z*-form of **3a** could be separated easily. Heating of pure **3a**-*E* in acetic acid afforded a mixture of **4a**[6] and **5a**[6] (Scheme 2). The yield of desired 3-(benzylidene)-1,5-benzodiazepin-2-one (**4a**) was moderate (36%). Instead, the benzimidazole-substituted compound **5a** was isolated in 34% yield.

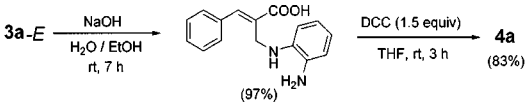
To improve the yield of the desired benzodiazepine



Scheme 1



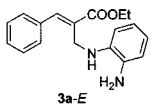
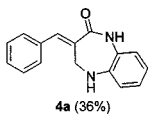
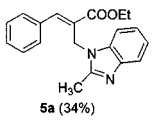
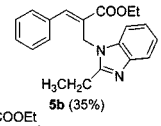
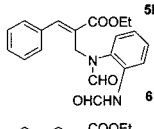
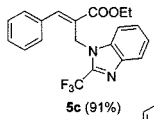
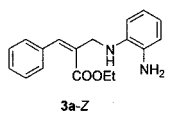
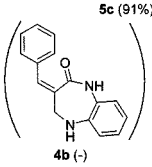
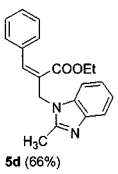
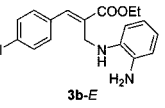
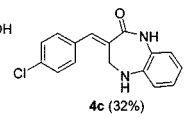
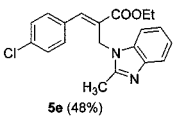
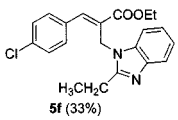
Scheme 2



Scheme 3

derivative **4a**, we examined other carboxylic acid solvent such as propionic acid, formic acid and trifluoroacetic acid as shown in Table 1. However, we could not improve the yield of **4a**. In all cases, except for formic acid, differently substituted benzimidazole-substituted derivatives, **5b** and **5c**, were isolated in variable yields. It is interesting to note that the use of formic acid gave neither the corresponding benzodiazepine nor benzimidazole derivatives. Instead, di-

Table 1. Synthesis of 3-benzylidene-1,5-benzodiazepin-2-one derivatives

Entry	S_N2' product **3**	Conditions	Products (% yield)
1	 **3a**-*E*	CH_3COOH 60-70 °C 18 h	 **4a** (36%)  **5a** (34%)
2	**3a**-*E*	CH_3CH_2COOH 60-70 °C 20 h	**4a** (32%)  **5b** (35%)
3	**3a**-*E*	HCOOH rt 2 h	 **6** (73%)
4	**3a**-*E*	CF_3COOH 60-70 °C 2 h	 **5c** (91%)
5	 **3a**-*Z*	CH_3COOH 60-70 °C 24 h	 **4b** (-)  **5d** (66%)
6	 **3b**-*E*	CH_3COOH 60-70 °C 19 h	 **4c** (32%)  **5e** (48%)
7	**3b**-*E*	CH_3CH_2COOH 60-70 °C 19 h	**4c** (28%)  **5f** (33%)

formyl derivative **6** was formed in good yield. In formic acid *N*-formylation proceeded easily at the two nitrogen atoms, thus preventing the next cyclization toward benzodiazepine or benzimidazole.

The reaction of acetic acid and *Z*-form of **3a** gave the benzimidazole derivative **5d** as the sole product (66%, entry 5). We could not isolate the corresponding benzodiazepine compound **4b** at all. We could not explain the reason at this stage. The reaction of **3b**-*E* in acetic acid or in propionic acid gave the similar results (entries 6 and 7).

Improved synthesis of benzodiazepine derivative **4a** was finally carried out by using 1,3-dicyclohexylcarbodiimide (DCC) method for the amide bond formation. Hydrolysis of **3a**-*E* with sodium hydroxide gave the corresponding acid derivative in 97% yield. Formation of the amide bond by using DCC in THF (rt, 3h) afforded **4a** in 83% yield (Scheme 3).

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References and Notes

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4. Khan, M. H.; Bano, Q.; Nizamuddin *J. Agric. Food Chem*. **1995**, *43*, 2719.
5. Racker, R.; Doring, K.; Reiser, O. *J. Org. Chem*. **2000**, *65*, 6932.
6. A typical procedure for the synthesis of **3a**, **4a** and **5a**: A stirred solution of **1a** (496 mg, 2.0 mmol), phenylenediamine (**2a**, 432 mg, 4.0 mmol) and K_2CO_3 (552 mg, 4.0 mmol) in acetonitrile (10 mL) was heated to reflux for 14 h. After usual workup and column chromatographic separation (hexane/ether, 3:1) allylic substitution products **3a**-*E* (304 mg, 51%) and **3a**-*Z* (102 mg, 17%) was obtained. Pure **3a**-*E* (296 mg, 1.0 mmol) in acetic aicd (3 mL) was heated to 60-70 °C during 18 h. After usual workup and column chromatographic separation (hexane/ether, 3:1-1:2), **4a** (91 mg, 36%) and **5a** (110 mg, 34%) were isolated. **3a**-*E*: oil; IR (KBr) 3403, 3343, 3246, 1701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (t, J = 7.1 Hz, 3H), 3.50 (br s, 3H), 4.10 (s, 2H), 4.29 (q, J = 7.1 Hz, 2H), 6.55-6.78 (m, 4H), 7.33-7.46 (m, 5H), 7.91 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.27, 41.38, 61.10, 112.95, 116.19, 119.36, 120.23, 128.64, 129.09, 129.50, 129.73, 134.82, 135.25, 136.97, 142.56, 167.78. **3a**-*Z*: oil; IR (KBr) 3404, 3342, 3246, 1711 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11 (t, J = 7.2 Hz, 3H), 3.50 (br s, 3H), 4.10 (s, 2H), 4.15 (q, J = 7.2 Hz, 2H), 6.70-6.82 (m, 4H), 6.89 (s, 1H), 7.24-7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.74, 48.47, 60.82, 113.24, 116.64, 119.48, 120.56, 127.99, 128.03, 128.32, 131.74, 134.77, 134.82, 135.61, 136.73, 168.76. **4a**: yellow solid, mp 155-157 °C; IR (KBr) 3403, 3354, 3188, 3058, 1656, 1625, 1384 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.09 (br s, 1H, NH), 4.13 (s, 2H), 6.73-7.02 (m, 4H), 7.32-7.43 (m, 5H), 7.85 (s, 1H), 8.76 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 43.34, 118.00, 119.79, 120.25, 123.05, 126.65, 127.45 (2C by ^1H-^{13}C hetero-COSY), 128.46, 130.97, 134.32, 137.03, 138.31, 168.62; Mass (70 eV) *m/z* (rel. intensity) 119 (99), 134 (20), 173 (30), 221 (34), 250 (M^+, 100). **5a**: oil; IR (KBr) 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (t, J = 7.2 Hz, 3H), 2.54 (s, 3H), 4.06 (q, J = 7.2 Hz, 2H), 5.20 (s, 2H), 7.02-7.64 (m, 9H), 8.01 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.89, 14.21, 40.43, 61.24, 109.98, 118.78, 121.54, 121.73, 127.89, 128.91, 129.17, 129.39, 134.19, 135.09, 142.45, 142.83, 152.30, 166.08.