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High stereoselective cyclopropanation reaction of 3-acylcoumarins with α-bromoketones at room temperature

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Abstract. Reaction of 3-acylcoumarins with α-bromoketones in the presence of a base give the cyclopropane derivatives in good stereoselectivity and moderate yield. The reaction was carried out at room temperature in mixed solvents without exclusion of moisture or air.

Keywords. 3-Acylcoumarins; α-bromoketones; cyclopropanation; stereoselectivity.

1. Introduction

Cyclopropane units are a fundamental class of functional group that are the focus of many organic synthesis programs and perform a key structural role in a range of bioactive natural and non-natural molecules.[1] Recently, a number of processes have emerged that often provide excellent levels of both enantio and stereocontrol for the synthesis of cyclopropanes.[2,3]

The formation of cyclopropane derivatives in the reaction of activated alkenes with α-haloesters or analogous compounds in the presence of a base, as well as the mechanism and stereoselectivity of these reactions have been well studied.[4] Widmen found that the reaction of 3-acylcoumarins with phenacylchloride or phenacylbromide in the presence of sodium ethoxide resulted in the formation of cyclopropane products in low to moderate yields.[5] The groups of Nestor A. Rodios improved the yields by using a phase transfer systems and also gave an explanation of the stereoselectivity of these reactions.[6] But the stereoselectivity of the reaction products are not good in these reports. Here, we report a method to give the cyclopropane products in good stereoselectivity and moderate yields.

2. Experimental

Column chromatography was carried out on silica gel (200–300 mesh). ^{1}H NMR spectra were recorded on 300 MHz or 400 MHz in $CDCl_3$, chemical shifts are reported in ppm using TMS as internal standard. ^{13}C NMR spectra were recorded on a Varian 75 MHz or Varian 100 MHz spectrometers with complete proton decoupling. MS spectra were recorded by the EI method on a HP 5998 mass spectrometer.

3-Ethoxycarbonyl coumarins **1a** (44 mg, 0·2 mmol), phenacylbromide **2a** (40 mg, 0·2 mmol), powder NaOH (16 mg, 0·4 mmol), CH_3CN/THF (1 : 1) (2 mL) were successively added to a 5 mL flask, and then the mixture was stirred magnetically at room temperature for 2 h. H_2O (2 mL) was added to the mixture and extracted thrice with 15 mL of ethyl acetate. The combined extract was washed with H_2O and brine and then dried ($MgSO_4$). The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography on silica column to give the **3a**.

2.1 *Ethyl 4,5-benzo-endo-7-benzoyl-3-oxa-2-oxo-cis-bicyclo[4.1.0]hept-4-en-1-carboxylate (**3a**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 1·32 (*t*, 3H, J = 7·1 Hz) 3·42 (*d*, 1H, J = 9·6 Hz) 4·17 (*d*, 1H, J = 9·6 Hz) 4·27–4·33 (*m*, 2H) 6·96–7·12 (*m*, 2H) 7·20–7·29 (*m*, 2H) 7·38–7·47 (*m*, 2H) 7·51–7·60 (*m*, 1H) 7·87–7·92 (*m*, 2H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 13·92, 33·55, 33·99, 34·57, 63·05, 113·71, 116·66, 124·30, 128·26, 128·64, 128·69, 129·56, 133·86, 136·08, 151·43, 161·04, 167·26, 191·30 MS: 336 [M^+].

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2.2 *Methyl 4,5-benzo-endo-7-benzoyl-3-oxa-2-oxo-cis-bicyclo[4.1.0]hept-4-en-1-carboxylate* ***(3b)***

^{1}H NMR (300 MHz, $CDCl_3$): δ 3·46 (*d*, 1H, *J* = 9·6 Hz) 3·86 (*s*, 3H) 4·19 (*d*, 1H, *J* = 9·6 Hz) 7·02–7·05 (*m*, 1H) 7·09–7·12 (*m*, 1H) 7·23–7·30 (*m*, 2H) 7·41–7·46 (*m*, 2H) 7·55–7·57 (*m*, 1H) 7·90–7·93 (*m*, 2H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 33·70, 33·76, 34·78, 53·73, 113·61, 116·67, 124·36, 128·28, 128·63, 128·71, 129·62, 133·91, 136·02, 151·38, 161·04, 167·85, 191·20, MS: 322 [M^+].

2.3 *1-Acetyl-4, 5-benzo-endo-7-benzoyl-3-oxa-2-oxo-cis-bicyclo[4.1.0]hept-4-en-2-one* ***(3c)***

^{1}H NMR (300 MHz, CDCl3): δ 2·62 (*s*, 3H) 3·43 (*d*, 1H, *J* = 9·8 Hz) 4·15 (*d*, 1H, *J* = 9·8 Hz) 7·04–7·06 (*m*, 1H) 7·11–7·14 (*m*, 1H) 7·24–7·29 (*m*, 2H) 7·41–7·46 (*m*, 2H) 7·55–7·57 (*m*, 1H) 7·89–7·92 (*m*, 2H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 29·63, 35·45, 37·07, 40·17, 114·27, 116·68, 124·48, 128·34, 128·60, 128·73, 129·57, 133·93, 136·03, 151·16, 166·22, 191·31, 200·02, MS: 306 [M^+].

2.4 *4,5-benzo-1,endo-7-dibenzoyl-3-oxa-2-oxo-cis-bicyclo[4.1.0]hept-4-en-2-one* ***(3d)***

^{1}H NMR (300 MHz, $CDCl_3$): δ 3·46 (*d*, 1H, *J* = 9·6 Hz) 3·38 (*d*, 1H, *J* = 9·6 Hz) 7·04–7·10 (*m*, 1H) 7·12–7·15 (*m*, 1H) 7·23–7·28 (*m*, 2H) 7·34–7·40 (*m*, 4H) 7·44–7·49 (*m*, 2H) 7·57–7·62 (*m*, 2H) 7·52–7·85 (*m*, 2H) 7·96–7·97 (*m*, 2H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 32·99, 33·73, 39·81, 109·72, 113·82, 117·17, 124·78, 128·42, 128·58, 128·74, 128·92, 129·78, 133·84, 133·92, 134·93, 136·20, 151·24, 163·24, 191·13, 191·71, MS: 368 [M^+].

2.5 *Ethyl 4,5-benzo-endo-7-(p-methyl-benzoyl)-3-oxa-2-oxo-cis-bicyclo[4.1.0]hept-4-en-1-carboxylate* ***(3e)***

^{1}H NMR (300 MHz, $CDCl_3$): δ 1·37 (*t*, 3H, *J* = 7·2 Hz) 2·42 (*s*, 3H) 3·44 (*d*, 1H, *J* = 9·8 Hz) 4·19 (*d*, 1H, *J* = 9·8 Hz) 4·33–4·38 (*m*, 2H) 7·02–7·08 (*m*, 1H) 7·12–7·16 (*m*, 1H) 7·27–7·32 (*m*, 4H) 7·85–7·87 (*m*, 2H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 13·93, 21·68, 33·44, 33·87, 34·57, 63·01, 113·84, 116·64, 124·25, 128·40, 128·61, 129·36, 129·49, 133·64, 144·94, 151·43, 161·14, 167·37, 190·74, MS: 348 [M^+].

2.6 *Methyl 4,5-benzo-endo-7-(p-methyl-benzoyl)-3-oxa-2-oxo-cis-bicyclo[4.1.0]hept-4-en-1-carboxylate* ***(3f)***

^{1}H NMR (300 MHz, $CDCl_3$): δ 2·38 (*s*, 3H) 3·23 (*d*, 1H, *J* = 9·8 Hz) 3·85 (s, 3H) 4·16 (*d*, 1H, *J* = 9·8 Hz) 7·05–7·08 (*m*, 1H) 7·13–7·16 (*m*, 1H) 7·28–7·34 (*m*, 4H) 7·82–7·85 (*m*, 2H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 21·72, 33·45, 33·86, 34·58, 53·76, 113·76, 116·72, 124·32, 128·47, 128·61, 129·42, 129·59, 133·63, 145·01, 151·92, 161·15, 168·04, 190·64, MS: 334 [M^+].

2.7 *1-Acetyl-4,5-benzo-endo-7-(p-methyl-benzoyl)-3-oxa-2-oxo-cis-bicyclo[4.1.0]hept-4-en-2-one* ***(3g)***

^{1}H NMR (300 MHz, $CDCl_3$): δ 2·37 (*s*, 3H) 2·61 (*s*, 3H) 3·39 (*d*, 1H, *J* = 9·6 Hz) 4·12 (*d*, 1H, *J* = 9·6 Hz) 6·99–7·04 (*m*, 1H) 7·09–7·12 (*m*, 1H) 7·21–7·28 (*m*, 4H) 7·78–7·81 (*m*, 2H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 21·73, 29·71, 35·42, 37·19, 40·03, 114·37, 116·67, 124·45, 128·49, 128·59, 128·62, 129·43, 129·51, 133·53, 145·06, 151·11, 190·80, 200·24, MS: 318 [M^+].

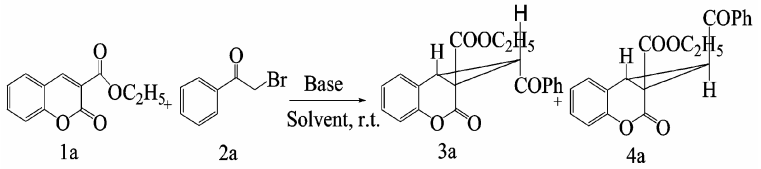
2.8 *Ethyl 4,5-benzo-endo-7-(p-bromo-benzoyl)-3-oxa-2-oxo-cis-bicyclo[4.1.0]hept-4-en-1-carboxylate* ***(3h)***

^{1}H NMR (300 MHz, $CDCl_3$): δ 1·33 (*t*, 3H, *J* = 6·9 Hz) 3·43 (*d*, ^{1}H, *J* = 9·6 Hz) 4·12 (*d*, 1H, *J* = 9·6 Hz) 4·28–4·38 (*m*, 2H) 7·02–7·08 (*m*, 1H) 7·09–7·11 (*m*, 1H) 7·21–7·29 (*m*, 2H) 7·56–7·58 (*m*, 2H) 7·76–7·79 (*m*, 2H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 13·95, 33·65, 34·09, 34·32, 63·18, 113·52, 116·73, 124·41, 128·49, 128·63, 129·32, 129·74, 132·06, 134·78, 151·43, 160·81, 167·15, 190·38, MS: 415 [M^+].

2.9 *Methyl 4,5-benzo-endo-7-(p-bromo-benzoyl)-3-oxa-2-oxo-cis-bicyclo[4.1.0]hept-4-en-1-carboxylate* ***(3i)***

^{1}H NMR (300 MHz, $CDCl_3$): δ 3·45 (*d*,1H, *J* = 9·6 Hz) 3·84 (*s*, 3H) 4·12 (*d*, 1H, *J* = 9·6 Hz) 7·02–7·11 (*m*, 2H) 7·23–7·28 (*m*, 2H) 7·55–7·58 (*m*, 2H) 7·74–7·77 (*m*, 2H) ^{13}C NMR (75 MHz, $CDCl_3$): 33·77, 33·84, 34·51, 53·81, 113·39, 116·71, 124·46, 128·47, 128·61, 129·35, 129·74, 132·06, 134·70, 151·35, 160·82, 167·71, 190·27, MS: 401 [M^+].

Table 1. Influence on yields and stereoselectivity with different solvents and bases.[a]



Entry	Base	Solvent	Time/h	Yield[b]/%	d.r.[c] (*cis* : *trans*)
1	K_2CO_3	MeCN	4	26	73 : 27
2	Cs_2CO_3	MeCN	4	28	69 : 31
3	NaOH	MeCN	2	33	>99 : 1
4	NaOH	DCE	2	32	>99 : 1
5	NaOH	THF	2	10	>99 : 1
6	NaOH	Et_2O	4	Trace[d]	>99 : 1
7	NaOH	CH_2Cl_2	4	Trace[d]	>99 : 1
8	NaOH	Acetone	4	52	>99 : 1
9	NaOH	MeCN/Et_2O (1 : 1)	2	54	>99 : 1
10	NaOH	MeCN/THF (1 : 1)	2	68	>99 : 1

[a]The reactions of 1 (0·2 mmol) with 2 (0·2 mmmol) were carried out in the presence of a base (0·4 mmol) in 2 mL solvents
[b]Isolated yield
[c]Determined by ^{1}H NMR spectroscopy
[d]Substrate can not be converted completely

2.10 *1-Acetyl-4,5-benzo-endo-7-(p-bromo-benzoyl)-3-oxa-2-oxo-cis-bicyclo[4.1.0]hept-4-en-2-one* ***(3j)***

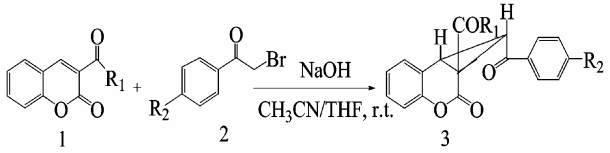
^{1}H NMR (300 MHz, $CDCl_3$): δ 2·51 (*s*, 3H) 3·41 (*d*, 1H, J = 9·6 Hz) 4·09 (*d*, 1H, J = 9·6 Hz) 7·03–7·12 (*m*, 2H) 7·24–7·27 (*m*, 2H) 7·54–7·57 (*m*, 2H) 7·73–7·76 (*m*, 2H) ^{13}C NMR (75 MHz, $CDCl_3$): 29·68, 35·56, 36·75, 40·11, 113·97, 116·69, 124·60, 128·55, 129·42, 129·70, 129·77, 132·09, 134·59, 163·70, 190·42, 199·96, MS: 385 [M^+].

3. Results and discussion

Based on previous research, we identified the optimized reaction conditions using 3-ethoxycarbonyl coumarin **1a** and phenacylbromide **2a** for the development of our method. 3-ethoxycarbonyl coumarin was treated with 1·0 equiv of phenacylbromide in the presence of 2·0 equiv of base in various solvents at room temperature. By screening bases it becomes apparent that K_2CO_3 or Cs_2CO_3 is not the valid base to give good stereoselectivity in MeCN. Accordingly, when NaOH was used as a base in MeCN, the *cis*-isomer **3a** was formed predominantly. Interestingly, strong base works more efficiently than the weak base (Entries 1–3 in table 1), and the most efficient base was found to be NaOH (Entry 3 in table 1). The yield can not be improved obviously by increasing the amount of the base. In order to improve the yields of the *cis*-isomer, different solvents were screened. From the result, we can see that the reactions proceeded slowly in Et_2O and CH_2Cl_2 at room temperature and the substrates can not be completely converted into the products (Entries 6, 7 in table 1). In MeCN and DCE, although the reactions completed within 2 h and no obvious by-product was found, low yields were observed. The reaction in mixed solvents, such as MeCN/Et_2O (1 : 1), MeCN/THF (1 : 1), and especially MeCN/THF (Entry 10), was better than other ones and needed no heating and long reaction time to give good yields. So MeCN/THF (1 : 1) was chosen as the most effective solvent for the reactions of α-bromoketones with 3-acylcoumarins at room temperature.

With optimized conditions in hand, we further investigated the reaction of different 3-acylcoumarins with α-bromoketones as shown in table 2. It shows the range of cyclopropanes that can be formed by this method. The results demonstrate that the reaction is applicable with many types of functionality and all examples produced *cis*-isomers totally (d.r. >99 : 1). In cases, the generation of *cis*-isomers was not greatly effected by changes in the R_1 group except that when R_1 was changed to a large group, a

Table 2. Scope of reaction.[a]



Entry	R_1	R_2	Product	Time/h	Yield[b]/%
1	OC_2H_5	H	**3a**	2	68
2	OCH_3	H	**3b**	2	64
3	CH_3	H	**3c**	2	40
4	Ph	H	**3d**	3	25[c]
5	OC_2H_5	CH_3	**3e**	2	50
6	OCH_3	CH_3	**3f**	2	51
7	CH_3	CH_3	**3g**	2	40
8	OC_2H_5	Br	**3h**	2	41
9	CH_3	Br	**3i**	2	54
10	CH_3	Br	**3j**	2	35

[a]For a detailed experimental operation, see experimental section
[b]Isolated yield. [c]1.5 equiv 2 was used

low yield was obtained because of steric hindrance (Entries 1–4). The stereoselectivity and the yields of the products were not strongly affected when α-bromoketones bearing electron-withdrawing or electron–donor substitutents were used (Entries 5–10). The *cis*-isomers were determined by ^{1}H NMR spectra. The structures of all compounds were determined by NMR spectra and MS data. The spectroscopic data of all compounds are in agreement with the proposed structures.

4. Conclusions

In summary, we have developed a general and efficient reaction to give the cyclopropane products in good stereoselectivity and moderate yields. The method is rapid and simple, without catalyst. It must be useful in synthesis of more natural compounds.

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