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Unexpected formation of new bicyclic γ-lactams by dimerization of α-chloroacetoacetanilides

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ABSTRACT

Novel and unusual dimerization reaction of α-chloroacetoacetanilide under basic reaction condition to give structurally unique 6-oxa-3-azabicyclo[3.1.0]hexane was described.

α-Substituted acetoacetanilides (α-haloacetoacetanilide or α-hydroxyacetoacetanilide) are one of the well-reviewed chemical intermediates and a versatile precursor for the synthesis of heterocyclic compounds.[1,2] Main chemical features of α-substituted acetoacetanilides include four reactive sites (two nucleophilic and two electrophilic) and derivatizable aryl ring site (e.g., phenyl ring). 5-Membered heterocyclic compounds from them, for example, thiazoles, imidazoles, oxathiins, and oxazoles, are very frequently found in marketed drugs, drug candidates, and many chemical libraries (see Fig. 1).

Previously, we reported the syntheses of new sulfur containing heterocycles and isomeric dihydro-1,4-oxathiin starting from

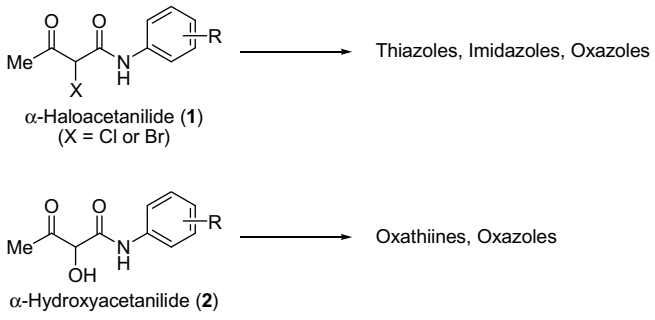

Figure 1. α-Substituted acetoacetanilides as a precursor for 5-membered heterocycles.

α-chloroacetoacetanilide.[3–5] Recently, our efforts were devoted to substitution reaction of α-chloroacetoacetanilide with various nucleophiles for the purpose of preparation of useful precursors for the heterocyclic scaffolds. In the course of trying to substitution reaction of 2-chloroacetoacetamide for the synthesis of 2-hydroxyacetoacetamide, unexpected formation of dimerized compounds from α-chloroacetoacetanilide was observed. Herein, we report a new finding of the novel formation of bicyclic γ-lactam derivatives from α-chloroacetoacetanilides in basic condition.

For the synthesis of 2-hydroxyacetoacetamide, the chloride of α-chloroacetoacetanilide (**3**) was successfully substituted with potassium acetate in the reaction condition of ethanol as solvent, 50 °C as reaction temperature, and open to air, to afford desired acetate **4** in good yield (86% chemical yield). In the course of this trial, careful observation could find additional small amount of new product (Scheme 1). To elucidate its structure, thorough analyses of spectral data (^{1}H NMR, ^{13}C NMR, Mass spectra) were carried out to reveal partial structural information. Its elemental analysis and mass spectrum showed the molecular formula of new product, $C_{20}H_{18}N_2O_5$, which is in agreement with that of the dimerized product with loss of two hydrogen chlorides and addition of one oxygen. The exact structure was confirmed through X-ray crystallographic analysis. The result revealed that dimerized products of α-chloroacetoacetanilide was further oxidized by molecular oxygen to give a finally epoxydized bicyclic γ-lactam **5** (Fig. 2).

As depicted in Table 1, our initial efforts were to uncover the generality of this unusual dimerization and to improve and optimize the chemical yields of the reaction. Various reaction conditions were screened. Instead of potassium acetate as base, potassium hydroxide, which is harder than potassium acetate

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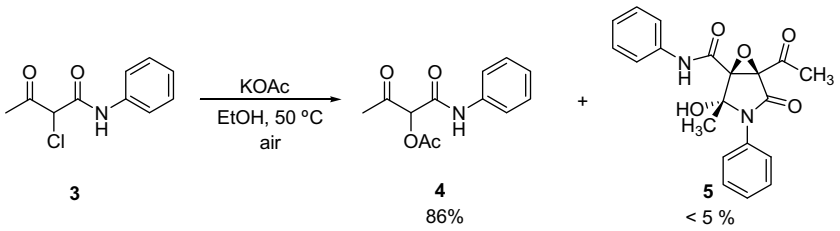


Scheme 1. Competitive reactions of substitution and dimerization.

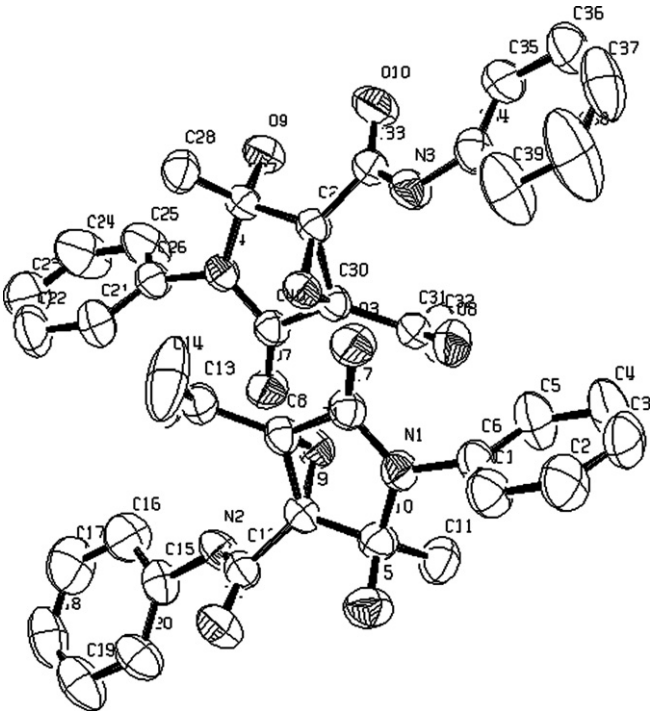
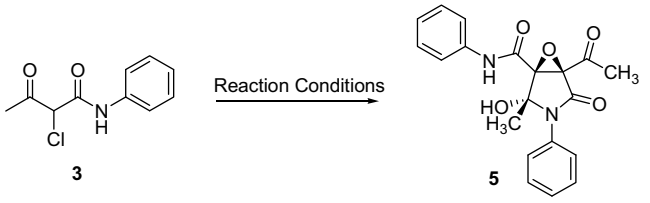


Figure 2. ORTEP plot of the structure of bicyclic γ-lactam in dimeric form. Hydrogens are excluded.

Table 1
Optimization of reaction condition for dimerization



Entry	Base	Reaction conditions	Yield[a] (%)
1	KOAc	EtOH, air, 50 °C, 7 h	<5
2	KOH	EtOH, air, 50 °C, 7 h	77
3	KOH	EtOH, O_2, 50 °C, 7 h	79
4	KOH	EtOH, N_2, 50 °C, 7 h	N.R.[b]
5	NaOH	EtOH, air, 50 °C, 7 h	74
6	Et_3N	EtOH, air, 50 °C, 7 h	<10
7	Pyridine	EtOH, air, 50 °C, 7 h	<10

[a] Isolated yields.
[b] No reaction.

and less nucleophilic, is used under the same reaction condition, and the chemical yields were dramatically improved (entries **2** and **3**). Bubbling oxygen gave almost same yield, compared to open to air condition. But, attempt to the same reaction under nitrogen atmosphere failed only to give complex mixtures including starting material, which suggested that the molecular oxygen was essentially involved in the reaction process. Sodium hydroxide delivered nearly the same yield as potassium hydroxide. Even when mild amine bases (triethylamine and pyridine) were used, detectable dimerized compounds were obtained though the yields were very low.

Though there are a few precedent papers on dimerization of ethyl acetoacetate,[7,8] it is the first finding of dimerization of α-chloroacetoacetanilide. The exact mechanism for this unusual dimerization is now unclear. However, increased yields were obtained in case the reaction was performed under oxygen atmosphere. One major by-product in the reaction was α-hydroxyacetanilide by nucleophilic substitution of chloride with hydroxide.

The starting α-chloroacetoacetanilides **3a–l** were readily prepared through the previously reported methods, as shown in Table 2.[6] Diketene and anilines in refluxing benzene afforded acetoanilides 7 in quantitative yields, followed by chlorination of acetoanilides by sulfuryl chloride in benzene at room temperature to give the desired products. Regardless of substituents on anilines, the manipulation of the process was very simple and overall yields were excellent.

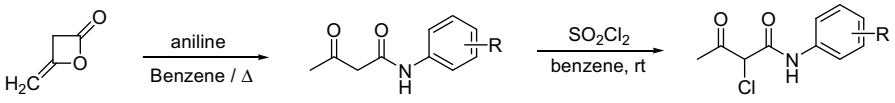
As shown in Table 3, dimerization reactions of α-chloroacetoacetanilides with various substituents on phenyl ring were carried out. The optimized, high-yielding procedure (EtOH/air/50 °C/7 h) afforded the desired dimerized products (**5a–l**), which were isolated by slow crystallization and absolutely pure enough for elemental analysis without further recrystallization. By virtue of easiness of preparation of starting materials, manipulation of reaction, and isolation of products, there were few problems even in scale-up process.

In summary, we have described the first finding of unusual dimerization/oxidation of α-chloroacetoacetanilide under basic reaction condition to give structurally unique 6-oxa-3-azabicyclo[3.1.0]hexane. The beneficial aspects of this reaction, that is, the easiness of preparation of starting materials, manipulation of reaction, and isolation of products allowed us to establish structurally unique chemical library. Further studies on their biological activities as well as for the scope and mechanism of the reaction are now in progress.

Typical procedure: Synthesis of compound **5**: To a solution of α-chloroacetoacetanilide **3** (42.3 g, 0.20 mol) in 95% ethanol (300 ml) at 50 °C was added a solution of 85% potassium hydroxide (11.2 g, 0.20 mol) in 95% ethanol dropwise over 80 min under air. The reaction mixture was stirred for 7 h. The white solid precipitates were filtered off and the solvent was removed to obtain a brown caramel. Crystallization of the resulting mixture with benzene gave a white crystal (27.8 g, 77%).

Spectroscopic and analytical data for compound **5a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.62 (s, 3H) 2.70 (s, 3H) 6.57 (s, 1H) 7.27–7.63 (m, 10H) 8.65 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 21.34, 29.74, 67.07, 67.45, 89.38, 120.46, 125.94, 127.33, 128.29, 129.18, 133.78, 135.50, 161.48, 165.24, 196.09. IR (KBr): 3450, 3335, 3246, 3086, 2980, 1728 (C=O), 1696 (C=O), 1594, 1542, 1480, 1400, 1310, 1144, 1048, 928, 876, 800, 760, 684 cm^{-1}. Elemental

Table 2
Synthesis of α-chloroacetoacetanilides from diketene

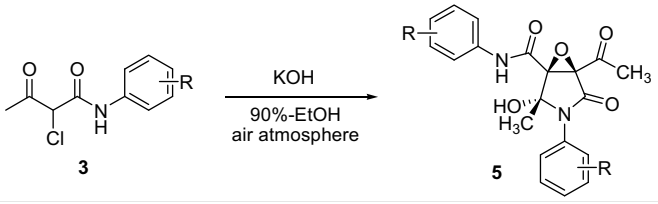


6 7 3

Entry	3	R	Yield[a] (%)	Entry	3	R	Yield[a] (%)
1	**3a**	H	85	7	**3g**	4-CH_3	80
2	**3b**	4-Br	88	8	**3h**	2-C_6H_5	87
3	**3c**	4-F	91	9	**3j**	2,4-DiCH_3	85
4	**3d**	2-Cl	89	10	**3k**	4-CN	79
5	**3e**	4-Cl	84	11	**3l**	2,6-DiCl	93
6	**3f**	3-Cl	89				

[a] Two-step yield.

Table 3
Dimerization of α-chloroacetoacetanilides



3 5

Entry	3	R_1	Mp (°C)	5, Yield (%)
1	**3a**	H	179–181	**5a**, 77
2	**3b**	4-Br	170–172	**5b**, 81
3	**3c**	4-F	174–176	**5c**, 73
4	**3d**	2-Cl	104–106	**5d**, 75
5	**3e**	4-Cl	188–192	**5e**, 78
6	**3f**	3-Cl	147–149	**5f**, 69
7	**3g**	4-CH_3	170–172	**5g**, 78
8	**3h**	2-C_6H_5	173–174	**5h**, 66
9	**3j**	2,4-DiCH_3	136–138	**5j**, 75
10	**3k**	4-CN	201–202	**5k**, 78
11	**3l**	2,6-DiCl	207–208	**5l**, 77

Anal. Calcd for $C_{20}H_{18}N_2O_5$: C, 65.57; H, 4.95; N, 7.65. Found: 65.37; H, 4.99; N, 7.61. HRMS (EI) calcd for $C_{20}H_{18}N_2O_5$ (M^+): 366.1216. Found: 366.1222.

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