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Reactivity of chloroacetylated β-enamino compounds. Synthesis of heterocycles

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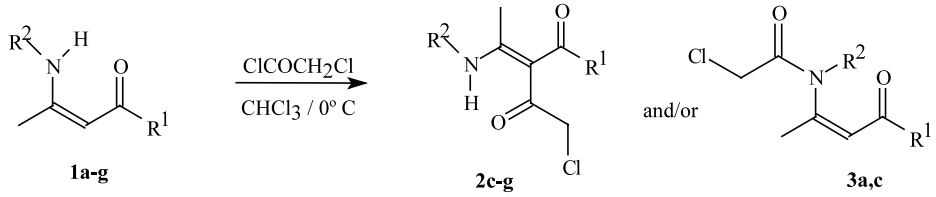
Abstract—Ethyl (*E*)-(3-amino substituted)-2-chloroacetyl-2-butenoates **2c**–**g**, *N*-[(*Z*)-1-methyl-3-oxo-1-butenyl]-2-chloroacetamide **3a** and ethyl (*Z*)-3-chloromethyl carboxamino-2-butenoate **3c**, have been prepared from β-amino α,β-unsaturated ketone **1a** and esters **1c**–**g** and chloroacetyl chloride. The reactivity of these compounds was studied by the reactions with binucleophiles, such as hydrazine and hydroxylamine, to evaluate the electrophilic centers in the formation of the polyfunctionalized heterocyclic compounds. © 2002 Published by Elsevier Science Ltd.

β-Enamino compounds are important compounds because they have found application as 1,3-bielectrophilic synthons in synthetic organic chemistry. Our research group have been exploring the methodologies suitable in the synthesis and reactivity of the β-enamino compounds and their derivatives.[1–7] The functionalization of these compounds by the introduction of different substituents on the nitrogen, the α-carbon[7] and the β-carbonylic carbon atoms has been studied by us, permitting the study of the reactivity of these systems using nucleophiles for the construction of heterocyclic compounds. Isoxazoles, for example, are important intermediaries in the synthesis of natural products[8] and pyrazoles are important ligands in metallo-organic chemistry,[9] and some of these compounds are used as components of drugs, herbicides and fungicides.

In order to study the reactivity of the β-enamino compounds with electrophiles, we used chloroacetyl chloride as a bielectrophile with a series of selected acyclic β-enamino compounds (**1a**–**g**), obtained using the methodology established by us, through reactions under a solid support, montmorillonite K-10, coupled with an ultrasound technique.[1,2,5] Chloroacetyl chloride permits the investigation of the competition at the nucleophilic centers, the α-carbonylic carbon and the nitrogen of the β-enamino compounds. There is also the possibility of attack of these nucleophilic centers at the *C*-sp^2 (C=O) or substitution in the *C*-sp^3 (-CH_2Cl) of the chloroacetyl chloride.

The reaction of β-enamino ketone **1a** (R^1 = Me, R^2 = H) with chloroacetyl chloride only afforded the *N*-chloroacetylated compound **3a**, while for the β-enamino ester **1c** (R^1 = OEt, R^2 = H) a mixture of *C*- and *N*-chloroacetylated products **2c** and **3c** was obtained in a 1:3 ratio. The difference of reactivity of the nucleophilic centers (*N*- and *C*-α) and the absence of steric effects on the nitrogen in the starting material probably influenced in the regiochemistry of this reaction. For the β-enamino esters **1d**–**g** the *C*-chloroacetylated compounds were isolated, demonstrating the influence of the substituent on the nitrogen in the formation of the products **2d**–**g** (Scheme 1). When **1b** (R^1 = Me, R^2 = Ph) reacts with chloroacetyl chloride under the same conditions,[10] the *N*-phenyl-2-chloroacetamide was isolated.



Scheme 1.

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For the reaction with **1e**, a mixture of **2e** and *N*-phenyl-2-chloroacetamide was obtained, by loss of the main skeleton of the β-enamino compound **1e**. After purification, **2e** was obtained as the minor (10%) product and *N*-phenyl-2-chloroacetamide was obtained as the major (60%) product. To prove the influence of the substituted group on the nitrogen, reaction of the β-enamino ester with a linked bulky group on the nitrogen (*i*-Pr) and chloroacetyl chloride was performed. Analysis of the reaction showed the formation of the *C*-chloroacetylated product only, confirming that steric factors have influenced the regiochemistry of the formed products (Table 1).

The reactivity of the chloroacetylated β-enamino compounds obtained **2c** and **2d** was studied by the reactions of these compounds with phenyl hydrazine, hydrazine and hydroxylamine, in order to evaluate the electrophilic centers in the formation of the polyfunctionalized heterocyclic compounds. The reaction of the **2c** or **2d** with phenyl hydrazine and hydrazine was carried out under reflux in ethanol[11] to give ethyl-6-methyl-4-oxo-2-phenyl-1,2,3,4-tetrahydro-5-pyridazinecarboxylate (**4**) and ethyl 5-chloromethyl-3-methyl-1*H*-4-pyrazolecarboxylate (**5**), respectively (Scheme 2).

The formation of **4** was unexpected and it can be considered to proceed by the attack of the unsubstituted nitrogen of the phenyl hydrazine to the β-carbon, followed by cyclization the other nitrogen to the methylenic carbon of the chloroacetyl chloride.

Table 1. Synthesis of chloroacetylated β-enamino compounds **2c–g** and **3a,c**

Compd	R^1	R^2	Yield[a] (%)	Mp (°C)
2c	OEt	H	15	131–132
2d	OEt	Me	60	49–51
2e	OEt	Ph	10	60–61
2f	OEt	Bn	35	Oil
2g	OEt	Allyl	30	83–85
3a	Me	H	70	68–69
3c	OEt	H	45	56–57

[a] Yield of pure isolated compounds.

Table 2. Synthesis of heterocyclic compounds **4–6**

Compd	Time (h)	Yield[a] (%)	Mp (°C)
4	24	15	128–132
5	16	35	Oil
6	4	45	Oil

[a] Yield of pure isolated compounds.

When **2c** or **2d** were treated with hydroxylamine hydrochloride, ethyl-5-chloromethyl 4-isoxazolecarboxylate (**6**) was isolated, independent of the substitution on the nitrogen in **2**, because the cyclization always proceeded with the loss of the amino group. This was also observed in the formation of the **5**. The structures of heterocycles **4–6** (Table 2) were confirmed by NMR spectral analysis.[12]

These results showed the versatility of chloroacetylated β-enamino compounds as building blocks to obtain polyfunctionalized heterocyclic compounds.

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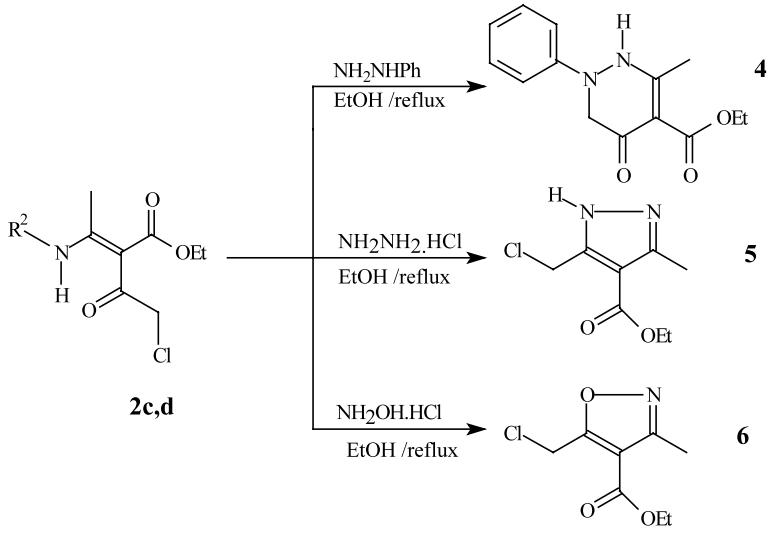

Scheme 2.

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10. *General experimental procedure for the preparation of* ***2c–g*** *and* ***3a,c***: β-Enamino compounds **1a–g** (9 mmol) were dissolved in chloroform (30 mL), cooled to −10°C and chloroacetyl chloride (21 mmol) was added dropwise. The solution was stirred at 0°C for 2–3 h, then neutralized with sodium carbonate, washed with water, dried over magnesium sulfate, filtered and the solvent was removed in vacuo to yield the crude products. Compounds **2d** and **3a** were purified by recrystallization from diisopropyl ether. Compounds **2e–g** were purified by column chromatography on silica gel (Vetec, 70–230 mesh) using 1% dichloromethane/ethyl acetate as eluent, resulting in the following yields of products: **2e** (10%), *N*-phenyl-2-chloroacetamide (60%), **2f** (35%), and **2g** (30%). The mixture of **2c** and **3c** was separated by filtration with hot hexane, affording solid **2c** (15%). The solvent was then evaporated, resulting in the formation of **3c** (45%).
11. Ethyl (*E*)-(3-amino substituted)-2-chloroacetyl-2-butenoates **2c** or **2d** (1 mmol) were mixed with phenyl hydrazine or hydrazine hydrochloride or hydroxylamine hydrochloride (2 mmol) in ethanol (2 mL). The mixture was refluxed for 24 h for to give **4**, 16 h to give **5** and 4 h to give **6**. These were extracted with ethyl acetate, then the organic layer was washed with water (3×10 mL), dried over magnesium sulfate, filtered and the solvent was removed in vacuo to yield the crude products. Product **4** was purified by recrystallization from diisopropyl ether, while compounds **5** and **6** were purified by column chromatography on silica gel (Vetec, 70–230 mesh) using 40% dichloromethane/ethyl acetate as eluent for **5** and 10% dichloromethane/ethyl acetate as eluent for **6**.
12. Selected spectral data for compound **4**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.46 (3H, t, CH_3, $J=7.0$), 2.53 (3H, s, CH_3), 4.34 (2H, q, CH_2, $J=7.0$), 4.70 (2H, s, CH_2), 7.26–7.52 (5H, m, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.7 (CH_3), 29.75 (CH_3), 55.72 (C-3), 65.25 (O-CH_2), 109.14 (C-5), 125.52 (C_{arom}), 128.82 (C_{arom}), 129.36 (C_{arom}), 137.92 (C_{arom}), 147.37 (C-6), 162.42 (C=O), 196.22 (C=O). Compound **5**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.38 (3H, t, CH_3, $J=7.0$), 2.53 (3H, s, CH_3), 4.34 (2H, q, CH_2, $J=7.0$), 4.86 (2H, s, CH_2), 9.0 (1H, br, NH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 11.88 (CH_3), 14.13 (CH_3), 37.53 (CH_2-Cl), 60.15 (O-CH_2), 108.76 (C-4), 146.52 (C-3), 149.66 (C-5), 163.55 (C=O). Compound **6**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40 (3H, t, CH_3, $J=7.0$), 2.47 (3H, s, CH_3), 4.37 (2H, q, CH_2, $J=7.0$), 4.89 (2H, s, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 11.28 (CH_3), 13.79 (CH_3), 33.21 (CH_2-Cl), 60.89 (O-CH_2), 109.72 (C-4), 159.79 (C-3), 160.87 (C=O), 170.95 (C-5).