A Convenient Method for the Synthesis of Six-membered Heterocyclic Enaminones

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Enaminones are widely employed in the synthesis of heterocycles, however heterocyclic enaminones and their use in the synthesis of more complex systems have been less studied. The reaction between 4-chloroacetylacetate and aliphatic or aromatic 1,2-aminoalcohols, 1,2-aminothiols or 1,2-diamines, yields in one pot a six-membered 1,4-heterocyclic system containing the enaminone moiety.

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The term enaminone was introduced by Greenhill [1] to define the enamine of a 1,3-diketone, β-ketoester or similar 1,3-difunctional reagents. Enaminones are useful and widely used building blocks in the synthesis of alicyclic, aromatic and heterocyclic compounds [2,3,4]. The most frequently used enaminones are those obtained from ammonia or alkylamines, but the reactivity of enaminones containing other functions as hydroxyl or thiol groups is less known.

A few heterocyclic enaminones (Figure 1) whose N and C_β atoms are placed in an heterocyclic ring have been reported. Example of such a class of compounds are cyclic ketene aminals (cyclic 1,1-enediamines) [5] or the 2-oxomorpholine enaminones used in the Nenitzescu's reaction for the synthesis of indole derivatives [3].

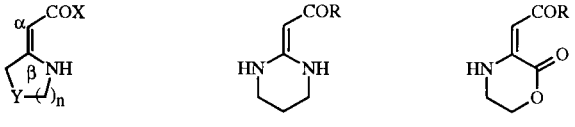


Figure 1. Heterocyclic enaminones.

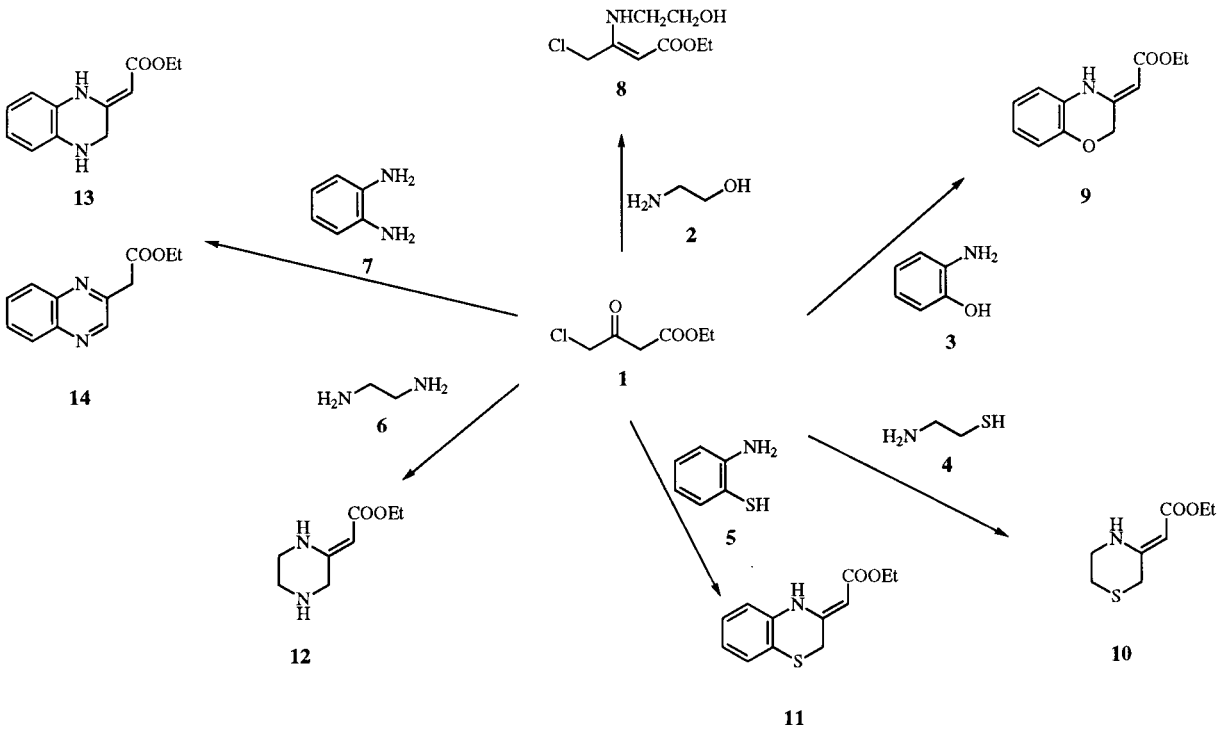
In preceeding papers, we described the synthesis of enaminones carrying OH or SH groups at the *N*-alkyl chain and their reactivity with Knoevenagel adducts [6,7,8]. The presence of these groups in the enaminone *N*-alkyl chain introduces a new nucleophilic center yielding bicyclic systems in a single process. A Michael addition accompanied by hetero-annulation was proposed for the formation of oxazolopyridines, thiazolopyridines and pyridooxazines. The long lasting antihypertensive activity showed by these compounds [9] prompted us to initiate the synthesis of more complex heterocyclic systems.

In order to study the utility of several oxazine, thiazine and diazine based enaminones for the synthesis of other heterocyclic systems, we prepared enaminones **8-13** (Scheme 1). The methodology used for this purpose was the reaction between ethyl 4-chloroacetylacetate (**1**) as a dielectrophilic reagent and the corresponding aminoderivative **2-7** as the dinucleophile. The reaction was mainly carried out at room temperature in methanol or tetrahydrofuran, though in some cases, the addition of triethylamine was neccesary to complete the cyclization, producing the enaminones in yields higher than 80%.

The heterocyclic enaminones **9-13** with oxazine, thiazine or pyrazine moieties were obtained in all the cases, but with ethanolamine only the acyclic enaminone **8** was obtained as a 3:1 mixture of the *E*/*Z* stereoisomers. The lower nucleophilic character of the oxygen atom prevents the deplacement of the chloride, even under a variety of conditions used to induce the cyclization. The intramolecular hydrogen bond in the major isomer (*Z*) and the differences in nmr shifts, allowed us to establish the stereochemistry for both stereoisomers (**8*Z*** ^{1}H-nmr: H_2 4.69, H_4 4.05, NH 9.10 ppm; **8*E*** ^{1}H-nmr H_2 4.64, H_4 4.91, NH 8.43 ppm). The 3:1 ratio is maintained without modification, even after reflux or the base treatment were carried out to induce the cyclization to the 1,4-oxazine system.

The reaction of **1** with *o*-aminophenol and some drops of triethylamine gave ethyl 3,4-dihydro-2*H*-1,4-benzoxazin-3-ylidenacetate (**9**) in 93% yield (^{1}H-nmr: OCH_2 4.57 s, H_2 4.68 s ppm). The hydrogen bond between the NH group and the carboxylic ester and the conjugation agree with the structure of the *E*-isomer, but not with that of the *Z*-isomer nor with the tautomer with an endocyclic double bond. The rigidity imposed by the benzene ring of the aminophenol and its higher nucleophilic character, accounts for the cyclization in this case, in contrast with the afore cited formation of compound **8**. In the same

Scheme 1



Preparation of enaminones **8-13** from **1**.

way, compounds **10-12** were obtained as single reaction products, and only the reaction with **7** gave a 1:1 mixture of **13** and the quinoxaline **14** due to the easy oxidation to the aromatic system. When the reaction was carried out under argon the amount of oxidized product decreased and **13** (60%) and **14** (20%) were isolated by chromatography.

As a conclusion, the reaction of the primary amines with ethyl 4-chloroacetate accompanied by intramolecular deplacement of the chlorine atom by the other heteroatom (O, S or N) of the amino reagent, is a very useful methodology for the preparation of heterocyclic enaminones in high yield. In preliminary assays, these reagents have proven to be good building blocks for the synthesis of polycyclic complex molecules.

EXPERIMENTAL

Melting points were measured on a Buchi 510 instrument and are uncorrected. The ^{1}H-nmr and ^{13}C-nmr were obtained on a Bruker WP 200 SY instrument, using deuteriochloroform as the solvent with tetramethylsilane as the internal standard. The ir spectra (FT) were recorded in dichloromethane film in a Nicolet (Impact 410) spectrophotometer. Mass spectra were recorded on a gc/ms Helwett-Packard 5890 Series II; chromatographic separations were accomplished on silica gel Merck 60 (0.063-0.2 mm), for flash chromatography an Eyela EF-10 apparatus was used, with 3-85 ml/minute flow rate, over silica gel Merck (0.040-0.063 mm); tlc was performed on precoated silica gel polyester plates (0.25 mm thickness) with fluorescent indicator uv 254 (Polychrom SI F_{254}). Elemental analyses were obtained in a Perkin-Elmer 2400 CHN elemental analyzer.

(*Z*)-Ethyl 4-Chloro-3-(2-hydroxyethylamino)crotonate (**8**) and (*E*)-Ethyl 4-Chloro-3-(2-hydroxyethylamino)-2-butenoate (**8'**).

A mixture of ethyl 4-chloroacetoacetate (1 mole) and aminoethanol (1 mole) in 20 ml of tetrahydrofuran was allowed to stand at room temperature for 24 hours. The solvent was removed and after flash chromatography (hexane/ethyl acetate 8:2), the mixture of enaminones **8** and **8'** was isolated in 85% yield.

Compound **8** had ^{1}H-nmr: δ 1.25 (m, 3H, Et, CH_3), 3.40 (m, 2H, H-1'), 3.80 (m, 2H, H-2'), 4.05 (s, 2H, H-4), 4.11 (m, 2H, Et, CH_2), 4.69 (s, 1H, H-2), 9.10 (bs, 1H, NH); ^{13}C-nmr: δ 14.3 (Et, CH_3), 42.2 (C-4), 44.8 (C-1'), 58.9 (Et, CH_2), 61.8 (C-2'), 85.1 (C-2), 158.0 (C-3), 170.4 (C-1).

Compound **8'** had ^{1}H-nmr: δ 1.25 (m, 3H, Et, CH_3), 3.40-4.10 (m, 4H, H-1' and H-2'), 4.11 (m, 2H, Et, CH_2), 4.64 (s, 1H, H-2), 4.91 (s, 2H, H-4), 8.43 (bs, 1H, NH); ^{13}C-nmr: δ 14.3 (Et, CH_3), 46.2 (C-1'), 48.0 (C-4), 60.6 (C-2'), 59.5 (Et, CH_2), 83.7 (C-2), 153.0 (C-3), 168.3 (C-1).

Ethyl 3,4-Dihydro-2*H*-1,4-benzoxazin-3-ylidenacetate (**9**).

A mixture of ethyl 4-chloroacetoacetate (1 mole) and *o*-aminophenol (1 mole) in 20 ml of methanol and some drops of triethylamine was allowed to stand at room temperature for 24 hours. The solution was washed with water/sodium chloride and evaporated to dryness. The enaminone **9** was directly obtained in 93% yield as a pure oily product; ^{1}H-nmr: δ 1.29 (t, J = 7.0 Hz, 3H, Et, CH_3), 4.18 (q, J = 7.0 Hz, 2H, Et, CH_2), 4.57 (s, 2H, H-2'), 4.68 (s, 1H, H-2), 6.80-7.00 (m, 4H, aromatic), 10.14 (m, 1H, NH); ^{13}C-nmr: δ 14.4 (Et, CH_3), 59.4 (Et, CH_2), 66.3 (C- 2'), 83.6 (C-2), 115.7 (C-5'), 116.7 (C-8'), 122.8 (C-6'), 122.8 (C-7'), 127.4 (C-4'a), 145.1 (C-8'a), 148.9 (C-3'), 170.1 (C-1); ir: ν 3308, 1664, 1626, 1608, 1502, 1035 cm^{-1}; ms: EI (m/z) 219 (M^+), 173.

Ethyl Perhydrothiazin-3-ylidenacetate (**10**).

Ethyl 4-chloroacetoacetate (1 mole) and 2-aminoethanethiol (3 moles) in 25 ml of methanol were allowed to stand at room temperature for 24 hours. The solvent was removed and after crystallization in $CHCl_3$/MeOH, the enaminone **10** was isolated in 90% yield as a white crystalline product, mp 58°; ^{1}H-nmr: δ 1.26 (t, J = 7.3 Hz, 3H, Et, CH_3), 2.93 (m, 2H, H-6'), 3.24 (s, 2H, H-2'), 3.53 (m, 2H, H-5'), 4.10 (q, J = 7.3 Hz, 2H, Et, CH_2), 4.55 (s, 1H, H-2), 8.61 (b, 1H, NH); ^{13}C-nmr: δ 14.6 (Et, CH_3), 27.9 (C-6'), 28.2 (C-2'), 40.3 (C-5'), 58.6 (Et, CH_2), 81.6 (C-2), 159.5 (C-3'), 170.6 (C-1); ir: ν 3336, 1652, 1629, 1149, 1099 cm^{-1}; ms: EI (m/z) 187 (M^+), 141.

Anal. Calcd. for $C_8H_{13}NO_2S$: C, 51.33; H, 6.95; N, 7.48. Found: C, 51.03; H, 6.64; N, 7.67.

Ethyl 3,4-Dihydro-2*H*-1,4-benzothiazin-3-ylidenacetate (**11**).

A mixture of ethyl 4-chloroacetoacetate (1 mole) and *o*-aminothiophenol (1.3 moles) in 25 ml of methanol was allowed to stand at room temperature for 24 hours. The solution was evaporated to dryness under reduced pressure and the enaminone **11** was obtained in a 76% yield as a yellow crystalline product, mp 64° (chloroform/diethyl ether); ^{1}H-nmr: δ 1.29 (t, J = 7.1 Hz, 3H, Et, CH_3), 3.39 (s, 2H, H-2'), 4.17 (q, J = 7.1 Hz, 2H, Et, CH_2), 4.68 (s, 1H, H-2), 6.80-7.20 (m, 4H, aromatic), 10.60 (b, 1H, NH); ^{13}C-nmr: δ 14.5 (Et, CH_3), 30.0 (C-2'), 59.4 (Et, CH_2), 85.6 (C-2), 117.6 (C-5'), 120.4 (C-8'a), 122.5 (C-8'), 127.2 (C-6'), 128.3 (C-7'), 136.4 (C-4'a), 150.4 (C-3'), 170.4 (C-1); ir: ν 3273, 1661, 1614, 1577, 975 cm^{-1}; ms: EI (m/z) 235 (M^+), 189.

Anal. Calcd. for $C_{12}H_{13}NO_2S$: C, 61.27; H, 5.53; N, 5.95. Found: C, 61.26; H, 5.37; N, 5.95.

Ethyl Piperazin-2-ylidenacetate (**12**).

A mixture of ethyl 4-chloroacetoacetate (1 mole) and ethylenediamine (1.5 moles) in 25 ml of methanol was allowed to stand at room temperature for 1 hour. The solution was evaporated to dryness under reduced pressure, and the enaminone **12** was obtained in 97% yield as an oily product; ^{1}H-nmr: δ 1.23 (t, J = 6.9 Hz, 3H, Et, CH_3), 3.08 (m, 2H, H-5'), 3.26 (m, 2H, H-6'), 3.54 (s, 2H, H-3'), 4.08 (q, J = 6.9 Hz, 2H, Et, CH_2), 4.32 (s, 1H, H-2), 8.62 (b, 1H, NH); ^{13}C-nmr: δ 14.5 (Et, CH_3), 41.5 (C-5'), 43.9 (C-6'), 47.5 (C-3'), 58.9 (Et, CH_2), 78.8 (C-2), 159.7 (C-2'), 170.6 (C-1); ir: ν 3308, 1730 (weak), 1650, 1600, 1170, 1049 cm^{-1}; ms: EI (m/z) 170 (M^+), 141, 124.

Ethyl 1,2,3,4-Tetrahydroquinoxalin-2-ylidenacetate (**13**) and Ethyl Quinoxalin-2-ylacetate (**14**).

A mixture of ethyl 4-chloroacetylacetate (1 mole) and phenylenediamine (1.3 moles) in 25 ml of methanol, was allowed to stand, under argon, at room temperature for 72 hours. After flash chromatography (hexane/ethyl acetate 9:1), compounds **13** and **14** were isolated in 60 and 20% yield respectively.

Compound **13** had ^{1}H-nmr: δ 1.28 (t, J = 6.9 Hz, 3H, Et, CH_3), 3.85 (s, 2H, H-3'), 4.16 (q, J = 6.9 Hz, 2H, Et, CH_2), 4.59 (s, 1H, H-2), 6.50-6.85 (m, 4H, aromatic), 10.29 (b, 1H, NH); ^{13}C-nmr: δ 14.4 (Et, CH_3), 44.3 (C-3'), 59.1 (Et, CH_2), 82.7 (C-2), 114.5 (C-5'), 115.5 (C-8'), 120.0 (C-6'), 122.4 (C-7'), 127.1 (C-8'a), 134.6 (C-4'a), 151.2 (C-2'), 170.4 (C-1); ir: ν 3370, 3294, 1731 (weak), 1650, 1506, 1160 cm^{-1}; ms: EI (m/z) 218 (M^+), 189, 171.

Compound **14** had ^{1}H-nmr: δ 1.28 (t, J = 6.9 Hz, 3H, Et, CH_3), 4.09 (s, 2H, H-2), 4.15 (q, J = 6.9 Hz, 2H, Et, CH_2), 7.73-8.30 (m, 4H, aromatic), 8.90 (s, 1H, H-3'); ^{13}C-nmr: δ 14.2 (Et, CH_3), 42.3 (C-2), 61.6 (Et, CH_2), 129.1 (C-5'), 129.3 (C-8'), 129.8 (C-6'), 130.2 (C-7'), 141.5 (C-4'a), 142.1 (C-8'a), 145.9 (C-2'), 149.9 (C-3'), 169.3 (C-1); ir: ν 1733, 1621, 1492, 1261, 1187 cm^{-1}; ms: EI (m/z) 216 (M^+), 187, 171, 144.

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