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SYNTHESIS OF ACETYL-SUBSTITUTED HETEROCYCLIC ENAMINES AND THEIR REACTION WITH DIETHYL AZODICARBOXYLATE

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Abstract: Acetyl-substituted heterocyclic enamines **4** were synthesized from lactim ethers **2** and acetylacetone through condensation and deacetylation reactions, and they, along with the ester-substituted heterocyclic enamines **6**, reacted with diethyl azodicarboxylate to afford *C*-adducts **7** and **8** in excellent yields.

Heterocyclic enamines, described as **1**, are the versatile building blocks for the synthesis of natural products,[1-3] especially of alkaloids such as pyrrolizidines,[4] indolizidines,[5,6] and quinolizidines.[7,8] In the presence of a strong base, heterocyclic enamines can undergo *C*-alkylation with halides,[2,9] ethyl bromoacetate[4] and methyl acrylate,[7] and consecutive intramolecular cyclocondensation between secondary amino moiety and ester group lead to fused heterocycles.[4,7]

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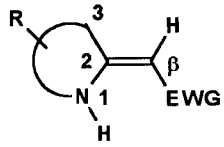


1

EWG = CN, COR', CO_2R' ·····

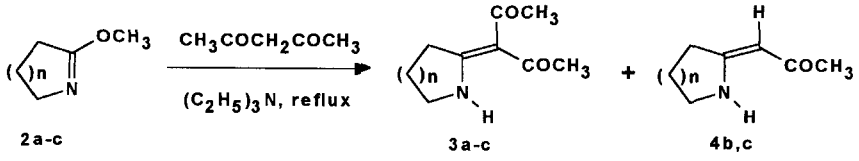
The syntheses of these *exo*-cyclic secondary enamines have been developed during the past three decades, among which the strategy based on the condensation of lactim ethers and active methylene compounds is mostly used.[10] The nitrile- substituted heterocyclic enamines (**1**, EWG=CN), for instance, were prepared from the reaction between lactim ethers and cyanoacetic acid esters followed by decarboxylation.[1] Another example is the synthesis of ester-substituted heterocyclic enamines (**1**, EWG=CO_2R') from the condensation of lactim ethers with acetoacetate or Meldrum's acid followed by deacylation or decarboxylation and transesterification steps, respectively.[11, 12] Recently, heterocyclic enamines bearing a lactone moiety have been prepared similarly by condensing 2-acetylbutyrolactones and lactim ethers.[13]

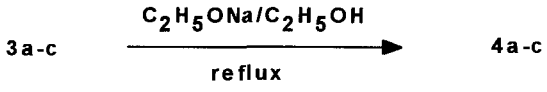
The methods reported in literature for the synthesis of acyl-substituted heterocyclic enamines, however, are not so satisfactory. Decarboxylation of *exo*-cyclic enaminoketoeters that are obtained from the condensation between acetoacetic acid esters and lactim ethers needs either drastic acid such as trifluroacetic acid[11] or elevated temperature (220°C).[14] While a sulfur extraction procedure developed by Eschenmoser and co-workers[15] requires the preparation of α-halomethyl ketones and thiolactams. It has been also reported that the acyl-substituted heterocyclic enamines are unstable.[11]

Here, we wish to report a general and facile method for the synthesis of the acetyl-substituted heterocyclic enamines. The reaction of these enamines, along

with the ester-substituted analogues with diethyl azodicarboxylate will also be described.

In contrast to the methods reported,[11,14,15] acetyl-substituted heterocyclic enamines were synthesized conveniently from acetylacetone and lactim ethers under very mild conditions. Acetylacetone reacted with 2-methoxy-pyrrolidine **2a** in refluxing triethylamine under nitrogen to give condensed product **3a** in moderate yield. Same reaction between acetylacetone and six- and seven-membered lactim ethers **2b,c,** however, afforded compounds **3b,c**, as well as the deacetylation products **4b,c** in total yields of 51-64%. The ratio of **3b,c** to **4b,c** is about 1:1. Deacetylation reaction of **3** proceeded smoothly in basic media[16] to give **4** in excellent yields.





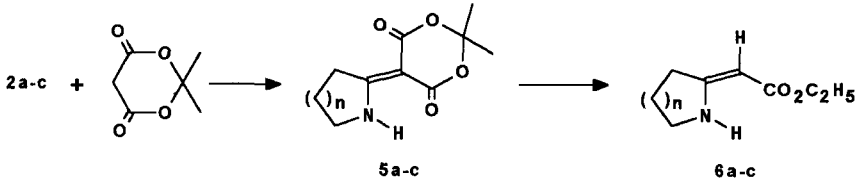
3a-c → 4a-c

2-4 a: n=1, **b**: n=2, **c**: n=3

Ester-substituted heterocyclic enamines **6** were prepared on the basis of a method reported in Lit.,[12] but with some variations. Thus, in the presence of catalytic amount of piperidine, compounds **5** were obtained from lactim ethers **2** and isopropylidene malonate in high yield. Decarboxylation and transesterification of **5** led to monoester-substituted products **6**.[12]

It is noteworthy that the rate of deacetylation and decarboxylation reactions is strongly dependent on the ring size of nitrogen-containing

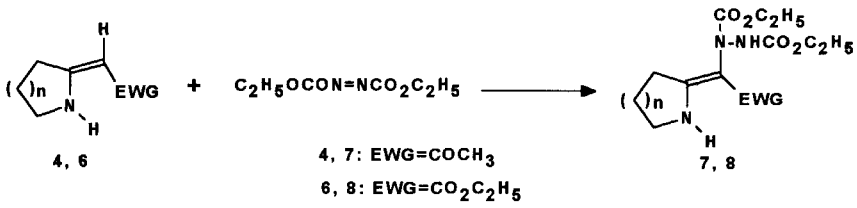
heterocycles. Larger rings make these reactions much easier, evidenced by the examples of **3b** and **3c** that underwent deacetylation spontaneously during the condensation reaction. On the other hand, smaller ring compound such as **5a** took long time and could not complete decarboxylation. The ring size effect may be attributed to the 1,2-A strain between carbonyl group and methylene moiety of C-3. The severe 1,2-A strain in seven-membered heterocycles results in the facile deacetylation and decarboxylation.



5, 6 a: n=1, **b**: n=2, **c**: n=3

In ^{1}H-NMR spectra, the chemical shifts of olefinic protons of acetyl- and ethoxycarbonyl-substituted heterocyclic enamines **4** and **6** range at 4.86-5.11 and 4.34-4.51 ppm, respectively. ^{13}C-NMR spectra of these compounds show that the β-carbon resonates at *ca.* 76-94 ppm, while the signal corresponding to carbon-2 appears at *ca.* 162-169 ppm. These mean the palorization of the double bond, and indicate that the electron density on the β-carbon is higher. The greater enaminic reactivity of heterocyclic enamines, therefore, would be expected. To examine their chemical properties, the reaction of **4** and **6** with an electron-deficient reagent diethyl azodcarboxylate was carried out.

Enamines **4** and **6** reacted smoothly in refluxing ethanol with diethyl azodicarboxylate, and *C*-adducts **7** and **8** were obtained in excellent yields. No cyclization was observed.



4, 6

4, 7: EWG=$COCH_3$

6, 8: EWG=$CO_2C_2H_5$

7, 8

The constitutions of **7** and **8** were confirmed by the mass spectra and elemental analyses. The observation of two amino protons and the disappearance of the olefinic proton signal in ^{1}H-NMR spectra excluded the possible [2+2], [2+4] and *N*-adducts, products being encountered commonly in the case of enamines.[17] The *E*-configutation of the double bond was assigned to the produts **7a-c** and **8b,c** because of the strong intramolecular hydrogen bonding between secondary amino groups and electron-withdrawing groups which was indicated by the downfield shift of the amino protons in ^{1}H-NMR spectra. In the case of **8a**, a mixture of *E*- and *Z*- conformers was observed and the ratio of them, measured roughly by ^{1}H-NMR spectra, was about 3 : 2. The outcome of this reaction demonstrates that heterocyclic enamines are good nucleophiles with the nucleophilicity of β-carbon being greater than that of the secondary amino group under neutral conditions.

EXPERIMENTAL

Melting points are uncorrected. Microanalyses were carried out by the Analytical Laboratory of the Institute. Mass spectra were obtained on a AEI MS-50 instrument. IR spectra were recorded on a Perkin-Elmer 782 spectrometer for KBr tablets. ^{1}H-NMR spectra of $CDCl_3$ solutions were measured by Varian Unity 200 and Bruker ARX-300 spectrometers. ^{13}C-NMR spectra of $CDCl_3$ solutions were recorded on a Jeol FX-100 spectrometer. The chemical shifts are reported in ppm downfield from Me_4Si.

Lactim ethers **2a-c** were prepared according to Lit.[9]

3-(2-Pyrrolidinylidene)pentan-2, 4-dione (3a):

A mixture of **2a** (0.09 mole, 9g) and acetylacetone (0.09 mole, 9g) in 30 ml of thiethylamine was refluxed under nitrogen for 2 days. After removal of triethylamine under reduced pressure, the residue was recrystallized in petroleum ether (60-90°C) / ethyl acetate to give 6.8g of **3a** (45 %) as colorless needles. m.p. 85-87°C (87°C[18]). MS: *m/z* = 167 (M^+, 38), 152 (52), 10 (100). IR: ν = 3175 (NH) , 1612, 1585 (CO), 1541 cm^{-1}. ^{1}H-NMR: δ = 11.50 (br, s, 1H, NH), 3.64 (t, 2H), 3.06 (t, 2H), 2.35 (s, 6H), 2.03 (quin, 2H). Anal. calc. for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found C, 64.40; H, 7.57; N, 8.29.

3-(Hexahydro-2-pyridinylidene)pentan-2, 4- dione (3b):

As **3a**. The residue was chromatographied on a silica gel column and eluted with a mixture of petroleum ether (60-90°C) / ethyl acetate (2:1). **3b** was obtained as colorless crystals. Yield: 26 %, m.p. 52.5-53°C (54°C[18]). MS: *m/z* = 181 (M^+, 40), 166 (67), 124 (100). IR: ν = 3160 (NH), 1640, 1590 (CO), 1559 cm^{-1}. ^{1}H-NMR: δ = 12.73 (br, s, 1H, NH), 3.43 (t, 2H), 2.60 (t, 2H), 2.27 (s, 6H), 1.67-1.88 ppm (m, 4H). Anal. calc. for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found C, 66.26; H, 8.20; N, 7.79.

4b (25%) was also separated as pale yellow liquid.

3-(Hexahydro-2-azepinylidene)pentan-2,4-dione (3c):

As **3b**. **3c** was obtained as colorless crystals. Yield: 31 %, m.p. 66.5-67.8°C. MS: *m/z* = 195 (M+, 34), 180 (45), 152 (66), 138 (100). IR: ν = 3155 (NH), 1659, 1590 (CO), 1568 cm^{-1}. ^{1}H-NMR: δ = 12.27 (br, s, 1H, NH), 3.30-3.51 (m, 2H), 2.36-2.48 (m, 2H), 2.25 (s, 6H), 1.63-1.83 ppm (m, 6H). Anal.

calc. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found C, 67.44; H, 8.94; N, 7.17.

4c (33%) was also separated as pale yellow liquid.

*General Procedure for the Synthesis of **4**:*

A solution of **3** (10 mmole) and sodium ethoxide (1.8 mmole) in 50 ml of absolute ethanol was refluxed for 18 hr. Precipitate was filtered off and the filtrate, after removal of solvent, was chromatographied on a silica gel column using an eluent of petroleum ether (60-90°C) / ethyl acetate (2:1) to give products **4**.

*2-(Acetylmethylene)pyrrolidine (**4a**):*

Colorless crystals. Yield: 90 %, m.p. 52-55°C. MS: *m/z* = 125 (M^+, 36), 110 (100). IR: ν = 3258 (NH), 1611 (CO), 1545 cm^{-1}. ^{1}H-NMR: δ = 9.82 (s, 1H, NH), 5.11 (s, 1H), 3.58 (t, 2H), 2.60 (t, 6H), 2.04 (s, 3H), 1.99 (quin, 2H). ^{13}C-NMR: δ = 193.7, 166.9, 89.0, 46.8, 31.6, 27.6, 20.5. Anal. calc. for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19. Found C, 66.86; H, 8.66; N, 10.87.

4a has been reported by the decarboxylation of *exo*-cyclic enaminoketoester in the yield of 50%.[14]

*2-(Acetylmethylene)hexahydropyridine (**4b**):*

Pale yellow oil and solidified when keeping it in refrigerator. Yield: 93 %. MS: *m/z* = 139 (M^+,42), 124 (100). IR: ν = 3225 (NH), 1610 (CO), 1578 cm^{-1}. ^{1}H-NMR: δ = 11.10 (s, 1H, NH), 4.86 (s, 1H), 3.34 (t, 2H), 2.35 (t, 2H), 1.98 (s, 3H), 1.69-1.83 (m, 4H). ^{13}C-NMR: δ = 193.7, 162.4, 94.4, 41.8, 32.7, 28.9, 27.9, 21.4. Exact mass: 139.1001. $C_8H_{13}NO$ requires 139.0996.

4b has been reported by the decarboxylation of *exo*-cyclic enaminoketoester in the yield of 43%.[14]

*2-(Acetylmethylene)hexahydroazepine (**4c**):*

Pale yellow oil. Yield: 90 %. MS: *m/z* = 153 (M^+, 13), 138 (34), 127 (30), 44 (100). IR: ν = 3210 (NH), 1610 (CO), 1580 cm^{-1}. ^{1}H-NMR: δ = 10.95 (s, 1H, NH), 4.96 (s, 1H), 3.34-3.38 (m, 2H), 2.50-2.55 (m, 3H), 2.00 (s, 3H), 1.60-1.81 (m, 6H). ^{13}C-NMR: δ = 194.2, 169.0, 93.4, 43.5, 34.1, 29.9, 28.8, 28.0, 25.2. Exact mass: 153.1160. $C_9H_{15}NO$ requires 153.1153.

4c has been reported by the decarboxylation of *exo*-cyclic enaminoketoester in the yield of 39%.[14]

*Isopropylidene (hexahydro-2-pyridinylidene)malonate (**5b**):*

To a mixture of **2b** (0.113 mole), isopropylidene malonate (0.12 mole) and triethylamine (50 ml) in 130 ml of benzene, 3 ml of piperidine was add. Refluxing under nitrogen for one day, 23 g of **5b** (90 %) was obtained after removal of solvents and recrystallization in ethanol. m.p. 114-116°C (116°C).[12]

5b has been prepared in the yield of 76% without using piperidine.[12]

5a and **5c** were synthesized according to Lit.[12]

Ester-substituted heterocyclic enamines **6** were prepared according to Lit.[12]

*2-(Ethoxycarbonylmethylene)pyrrolidine (**6a**):*

Yield: 84%, m.p. 61-62 °C (62°C).[12] MS: *m/z* = 153 (M^+, 38), 110 (100), 83 (64). IR: ν = 3345 (NH), 1650 (OCO), 1587 cm^{-1}. ^{1}H-NMR: δ = 7.85

(s, 1H, NH), 4.51 (s, 1H), 4.11 (q, 2H), 3.54 (t, 2H), 2.60 (t, 2H), 1.99 (quin, 2H), 1.26 (t, 3H). ^{13}C-NMR: δ = 170.5, 166.5, 76.5, 58.3, 47.0, 32.1, 21.9, 14.6. Anal. calc. for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found C, 61.79; H, 8.07; N, 8.87.

*2-(Ethoxycarbonylmethylene)hexahydropyridine (**6b**):*

Yield: 86%, pale yellow oil and solidified when keeping it in refrigerator. MS: *m/z* = 169 (M^+, 44), 124 (93), 97 (100). IR: ν = 3280 (NH), 1638 (OCO), 1600 cm^{-1}. ^{1}H-NMR: δ = 8.71 (s, 1H, NH), 4.34 (s, 1H), 4.07 (q, 2H), 3.30 (dt, 2H), 2.35 (t, 2H), 1.62-1.83 (m, 4H), 1.24 (t, 3H). ^{13}C-NMR: δ = 169.8, 161.8, 79.6, 57.3, 40.6, 28.4, 22.2, 19.4, 14.1. Anal. calc. for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found C, 63.82; H, 9.21; N, 8.35.

*2-(Ethoxycarbonylmethylene)hexahydroazepine (**6c**):*

Yield: 93%, m.p. 49-50.5°C (49°C)[12]. MS: *m/z* = 183 (M^+, 38), 138 (58), 110 (100), 96 (22). IR: ν = 3299 (NH), 1637 (OCO), 1590 cm^{-1}. ^{1}H-NMR: δ = 8.92 (s, 1H, NH), 4.42 (s, 1H), 4.10 (q, 2H), 3.32 (dt, 2H), 2.28-2.33 (m, 2H), 1.55-1.74 (m, 6H), 1.25 (t, 3H). ^{13}C-NMR: δ = 170.6, 168.3, 80.6, 58.0, 44.0, 34.9, 30.3, 30.0, 26.3, 14.5. Anal. calc. for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found C, 65.31; H, 9.60; N, 7.89.

General Procedure for the Synthesis of 7 and 8:

A solution of 2 mmole of **4** or **6** and 2 mmole of diethyl azodicarboxylate in 15 ml of absolute ethanol was refluxed for 3-6 hrs. After removal of solvent under vacuum, the residue was recrystallized in *n*-hexane / ethyl acetate to give colorless crystals.

Diethyl (E)-1-[acetyl(2-pyrrolidinylidene)methyl]-1,2-hydrazinedicarboxylate (7a):

Yield: 92%, m.p. 132-134°C. MS: *m/z* = 299 (M^+, 37), 211 (72), 180 (21), 139 (33), 126 (73), 112 (28), 95(100). IR: ν = 3250 (NH), 1740, 1685 (OCO), 1611 (CO), 1544, 1518, 1240, 1062 cm^{-1}. ^{1}H-NMR: δ = 9.96 (s, 1H, NH), 6.87 (s, 1H, NH), 4.19 (q, 4H), 3.68 (dt, 2H), 2.71-3.29 (m, 2H), 2.02-2.38 (m, 2H), 2.10 (s, 3H), 1.31 (t, 3H), 1.25 (t, 3H). Anal. calc. for $C_{13}H_{21}N_3O_5$: C, 52.16; H, 7.07; N, 14.04. Found C, 52.30; H, 6.99; N, 13.69.

Diethyl (E)-1-[acetyl(hexahydro-2-pyridinylidene)methyl]-1,2-hydrazinedicarboxylate (7b):

Yield: 91%, m.p. 158-159°C. MS: *m/z* = 313 (M^+, 23), 225 (100), 194 (11), 179 (34), 152 (17), 136 (25), 107(47). IR: ν = 3260 (NH), 1745, 1688 (OCO), 1596 (CO), 1572, 1511, 1241, 1053 cm^{-1}. ^{1}H-NMR: δ = 11.69 (s, 1H, NH), 6.86 (s, 1H, NH), 4.19 (q, 4H), 3.39 (dt, 2H), 2.41-3.10 (m, 2H), 2.11 (s, 3H), 1.73-1.88 (m, 4H), 1.32 (t, 3H), 1.29 (t, 3H). Anal. calc. for $C_{14}H_{23}N_3O_5$: C, 53.66; H, 7.40; N, 13.41. Found C, 53.65; H, 7.48; N, 13.34.

Diethyl (E)-1-[acetyl(Hexahydro-2-azepinylidene)methyl]-1,2-hydrazinedicarboxylate (7c):

Yield: 96%, m.p. 141-142°C. MS: *m/z* = 327 (M^+, 24), 239 (100), 193 (28), 150 (16), 123 (33), 96 (40). IR: ν = 3261 (NH), 1742, 1687 (OCO), 1598 (CO), 1571, 1511, 1245, 1055 cm^{-1}. ^{1}H-NMR: δ = 11.65 (s, 1H, NH), 6.88 (s, 1H, NH), 4.21 (q, 2H), 4.18 (q, 2H), 3.41 (dt, 2H), 2.70-2.95 (m, 2H), 2.11 (s, 3H), 1.56-1.77 (m, 6H), 1.32 (t, 3H), 1.29 (t, 3H). Anal. calc. for $C_{15}H_{25}N_3O_5$: C, 55.03; H, 7.70; N, 12.84. Found C, 54.89; H, 7.65; N, 12.60.

*Diethyl 1-[ethoxycarbonyl(2-pyrrolidinylidene)methyl]-1,2-hydrazinedicarboxylate (**8a**):*

Yield: 96%, m.p. 75.5-76.5°C. MS: *m/z* = 329 (M^+, 10), 256 (12), 241 (30), 169 (15), 123 (16), 110 (14), 95(100). IR: ν = 3341, 3280 (NH), 1739, 1711, 1660 (OCO), 1590, 1501, 1230, 1061 cm^{-1}. ^{1}H-NMR: δ = 7.96 (s, 0.6H, NH), 7.39 (s, 0.4H, NH), 6.99 (s, 0.4H, NH), 6.88 (s, 0.6H, NH), 4.07-4.23 (m, 6H), 3.47-3.60 (m, 2H), 2.72-3.19 (m, 2H), 1.96-2.11 (m, 2H), 1.22-1.30 (m, 9H). Anal. calc. for $C_{14}H_{23}N_3O_6$: C, 51.06; H, 7.04; N, 12.76. Found C, 50.92; H, 7.06; N, 12.67.

*Diethyl (E)-1-[ethoxycarbonyl(hexahydro-2-pyridinylidene)methyl]-1,2-hydrazinedicarboxylate (**8b**):*

Yield: 91%, m.p. 108-108.5°C. MS: *m/z* = 343 (M^+, 19), 270 (17), 255 (100), 224 (13), 209 (17), 183(14), 109 (62). IR: ν = 3280 (NH), 1732, 1700, 1637 (OCO), 1600, 1505, 1237, 1069 m^{-1}. ^{1}H-NMR: δ = 9.20 (s, 1H, NH), 6.89 (s, 1H, NH), 4.08-4.27 (m, 6H), 3.31 (dt, 2H), 2.17-3.66 (m, 2H), 1.63-1.84 (m, 4H), 1.30 (t, 3H), 1.29 (t, 3H), 1.28 (t, 3H). Anal. calc. for $C_{15}H_{25}N_3O_6$: C, 52.47; H, 7.34; N, 12.24. Found C, 51.89; H, 7.66; N, 12.18.

*Diethyl (E)-1-[ethoxycarbonyl(hexahydro-2-azepinylidene)methyl]-1,2-hydrazinedicarboxylate (**8c**):*

Yield: 93%, m.p. 97-99°C. MS: *m/z* = 357 (M^+, 21), 284 (18), 269 (100), 238 (10), 195 (15), 177 (16), 123 (26). IR: ν = 3285 (NH), 1740, 1700, 1639 (OCO), 1592, 1500, 1236, 1060 cm^{-1}. ^{1}H-NMR: δ = 9.30 (s, 1H, NH), 6.89 (s, 1H, NH), 4.18 (q, 6H), 3.37 (dt, 2H), 2.72-3.15 (m, 2H), 1.56-1.78 (m, 6H), 1.29 (t, 3H), 1.27 (t, 3H), 1.26 (t, 3H). Anal. calc. for $C_{16}H_{27}N_3O_6$: C, 53.77; H, 7.61; N, 11.76. Found C, 53.58; H, 7.68; N, 11.64.

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