# Synthesis of 6-Oxo-2,6-dihydro-4*H*-furo[3,4-*c*]pyrazoles and 6-Oxo-4*H*,6*H*-furo[3,4-*c*] [1,2]oxazoles from 2-Alkynyl Acetoacetates

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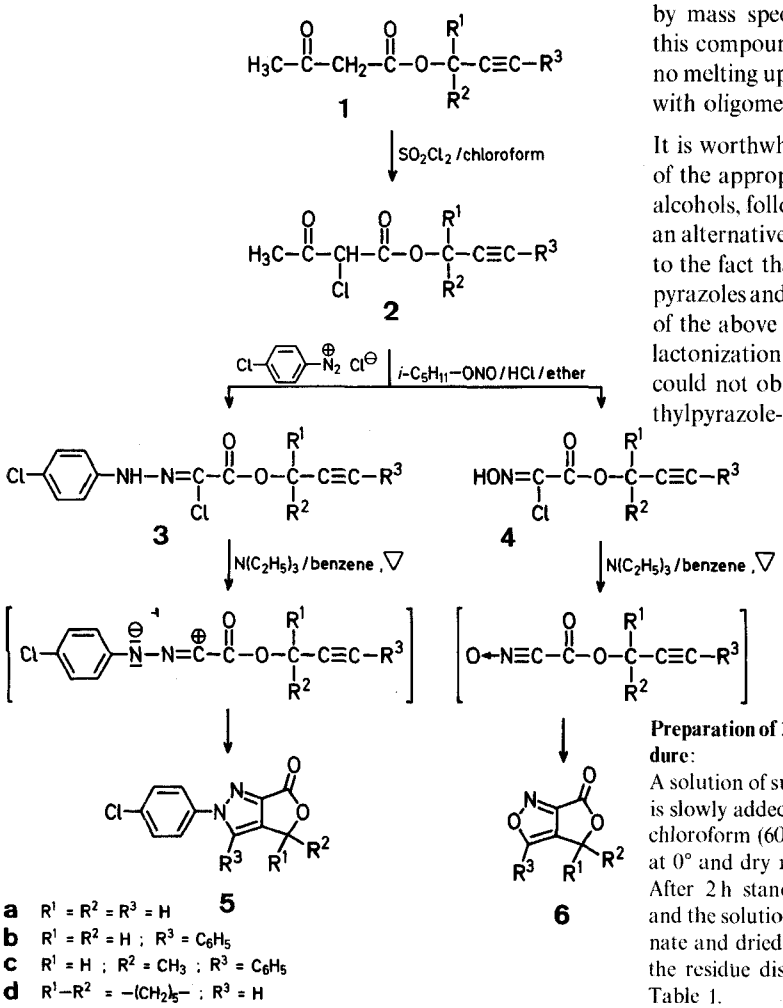
In the course of our studies on intramolecular 1,3-dipolar cycloadditions[1, 2, 3], we have found that the strained bicyclic systems **5** and **6** can be prepared starting from acetoacetic acid propargyl esters (**1**). This synthetic route involves (1) chlorination of the active methylene group in **1** to afford the chloroesters **2**, (2) introduction of a suitable function for generating *in situ* a 1,3-dipolar group, (3) intramolecular cycloaddition of the latter to the acetylenic bond. However, as illustrated in the Scheme, two different reaction sequences were used to prepare 6-oxo-2,6-dihydro-4*H*-furo[3,4-*c*]pyrazoles (**5**) and 6-oxo-4*H*,6*H*-furo[3,4-*c*] [1,2]oxazoles (**6**).

The coupling reaction of 4-chlorobenzenediazonium chloride with chloroesters **2** gave 2-chloro-2-(4-chlorophenylhydrazono)-acetic acid 2-alkynyl esters (**3**). Treatment of the latter with triethylamine afforded the fused pyrazole derivatives **5** as the predominating or exclusive products.

The reaction of chloroesters **2** with isoamyl nitrite produced 2-alkynyl 2-chloro-2-oximinoacetates (**4**). The latter were isolated as pure crystalline compounds with the exception of **4c**, obtained only as a crude oil; attempted distillation in vacuo and column chromatography on silica gel resulted in partial decomposition. Treatment of **4** with triethylamine led to a mixture of a few products, among which the 1,2-oxazole derivative **6** was present as the main component (T.L.C. analysis). In the case of **4a**, the desired product was isolated by column chromatography.

All compounds **5** and **6** exhibited correct elemental analyses, I.R., and N.M.R. spectra. For **5a**, the structure was confirmed by mass spectrometry; in fact, the physical properties of this compound (low solubility in the common solvents and no melting up to ~300°) might appear to be more consistent with oligomeric structures.

It is worthwhile to note that intermolecular cycloadditions of the appropriate nitrile imines and oxides with propargyl alcohols, followed by lactonization, could a priori represent an alternative route leading to **5** and **6**. However, in addition to the fact that 4-unsubstituted rather than 5-unsubstituted pyrazoles and 1,2-oxazoles are usually formed in the reaction of the above 1,3-dipoles with terminal triple bonds[4-7], the lactonization could encounter steric difficulties. In fact, we could not obtain **5a** from 1-(4-chlorophenyl)-4-hydroxymethylpyrazole-3-carboxylic acid[8].




**a** $R^1 = R^2 = R^3 = H$
**b** $R^1 = R^2 = H$ ; $R^3 = C_6H_5$
**c** $R^1 = H$ ; $R^2 = CH_3$ ; $R^3 = C_6H_5$
**d** $R^1-R^2 = -(CH_2)_5-$ ; $R^3 = H$

**Preparation of 2-Alkynyl 2-Chloroacetoacetates (2); General Procedure:**

A solution of sulfuryl chloride (66 mmol) in dry chloroform (20 ml) is slowly added (2 h) to a solution of the ester **1** (60 mmol) in dry chloroform (60 ml). During the addition, the temperature is kept at 0° and dry nitrogen is bubbled through the reaction mixture. After 2 h standing at room temperature, chloroform is added and the solution is washed with aqueous sodium hydrogen carbonate and dried with sodium sulfate. The solvent is removed and the residue distilled in vacuo to afford practically pure **2**. See Table 1.

**Table 1.** Preparation of Esters **1** and Chloroesters **2**[a]

| Product | Yield [%] | b.p. | $^1$H-N.M.R. ($CDCl_3$) $\delta$ [ppm][b, c] | | | | | Brutto formula[d] |
|---|---|---|---|---|---|---|---|---|
| | | | $H_3C-CO-$ | $CH_2$ or CHCl | $R^1$ | $R^2$ | $R^3$ | |
| **1b**[e] | 68 | 130–135°/0.5 torr | 2.24 (s) | 3.48 (s) | 4.95 (s) | | 7.3 (m) | $C_{13}H_{12}O_3$ (216.2) |
| **1c**[e] | 82 | 125–130°/0.1 torr | 2.25 (s) | 3.46 (s) | 5.72 (q) | 1.69 (d) | 7.3 (m) | $C_{14}H_{14}O_3$ (230.2) |
| **2a**[10] | 78 | 65–70°/0.5 torr | 2.41 (s) | 4.83 (s) | 4.83 (d)[f] | | 2.59 (t)[f] | $C_7H_7ClO_3$ (174.6) |
| **2b** | 52 | 132–137°/0.2 torr | 2.38 (s) | 4.83 (s) | 5.04 (s) | | 7.4 (m) | $C_{13}H_{11}ClO_3$ (250.7) |
| **2c** | 72 | 125–130°/0.2 torr | 2.38 (s) | 4.80 (s) | 5.78 (q) | 1.64 (d) | 7.4 (m) | $C_{14}H_{13}ClO_3$ (264.7) |
| **2d** | 74 | 118–123°/0.2 torr | 2.38 (s) | 4.72 (s) | 1.3–2.3 (m) | | 2.66 (s) | $C_{12}H_{15}ClO_3$ (242.7) |

[a] In the I.R. spectrum, all compounds gave a broad band at 1720–1770 $cm^{-1}$.
[b] At 60 MHz with TMS as the internal standard.
[c] The $^1$H-N.M.R. spectra showed the presence of ~10% of the enol form.
[d] The elemental analyses (C, H) of all compounds were in good agreement with the calculates values.
[e] Prepared according to the procedure reported for **1a, d.**[9]
[f] $J = 2.5$ Hz.

**Table 2.** Preparation of 1-Chloro-hydrazones **3** and 1-Chloro-oximes **4**

| Product | Yield [%] | m.p.[a] | I.R. (Nujol) $\nu$ [cm$^{-1}$] | $^1$H-N.M.R. ($CDCl_3$) $\delta$ (ppm) [b, c] | | | Brutto formula[d] |
|---|---|---|---|---|---|---|---|
| | | | | $R^1$ | $R^2$ | $R^3$ | |
| **3a** | 58 | 109° | 3210 (NH)<br>1710 (CO) | | 4.92 (d)[e] | 2.55 (t)[e] | $C_{11}H_8Cl_2N_2O_2$<br>(271.1) |
| **3b** | 66 | 138° | 3280 (NH)<br>1710 (CO) | | 5.16 (s) | 7.4 (m) | $C_{17}H_{12}Cl_2N_2O_2$<br>(347.2) |
| **3c** | 59 | 129° | 3270 (NH)<br>1725 (CO) | 5.85 (q) | 1.71 (d) | 7.3 (m) | $C_{18}H_{14}Cl_2N_2O_2$<br>(361.2) |
| **3d** | 53 | 111° | 3280 (NH)<br>1730 (CO) | | 1.3–2.3 (m) | 2.65 (s) | $C_{16}H_{16}Cl_2N_2O_2$<br>(339.2) |
| **4a** | 52 | 110–112° | 3300 (OH)<br>1725 (CO) | | 4.92 (d)[e] | 2.57 (t)[e] | $C_5H_4ClNO_3$<br>(161.5) |
| **4b** | 60 | 67–69° | 3300 (OH)<br>1750 (CO) | | 5.13 (s) | 7.4 (m) | $C_{11}H_8ClNO_3$<br>(237.6) |
| **4c** | 54 | [f] | 3300 (OH)<br>1750 (CO) | 5.83 (q) | 1.69 (d) | 7.3 (m) | |
| **4d** | 59 | 112–114° | 3300 (OH)<br>1720 (CO) | | 1.4–2.3 (m) | 2.69 (s) | $C_{10}H_{12}ClNO_3$<br>(229.7) |

[a] Uncorrected. Solvents for recrystallization: ethanol for **3**, tetrachloromethane for **4**.
[b] At 60 MHz with TMS as the internal standard.
[c] For **3**, broad singlet at $\delta = 8.35$–$8.40$ ppm (NH); for **4**, broad singlet in the range $\delta = 8$–$9$ ppm (OH).
[d] The elemental analyses (C, H, N) of all compounds were in good agreement with the calculated values.
[e] $J = 2.5$ Hz.
[f] Crude oil (85–90% purity, by N.M.R. analysis).

**Table 3.** Preparation of Fused Pyrazoles **5** and 1,2-Oxazoles **6**

| Product | Reaction time [h] | Yield [%] | m.p.[a] (recrystallized from) | I.R. (Nujol) $\nu_{CO}$ [cm$^{-1}$] | $^1$H-N.M.R. ($CDCl_3$) $\delta$ [ppm][b] | | | Brutto formula[c] |
|---|---|---|---|---|---|---|---|---|
| | | | | | $R^1$ | $R^2$ | $R^3$ | |
| **5a**[d] | 6 | 54 | dec. >280°[e]<br>(acetone) | 1760 | | 5.32 (d)[f] | 7.87 (t)[f] | $C_{11}H_7ClN_2O_2$<br>(234.6) |
| **5b** | 12 | 69 | 139°<br>(benzene) | 1770 | | 5.35 (s) | 7.3 (m) | $C_{17}H_{11}ClN_2O_2$<br>(310.7) |
| **5c** | 4 | 83 | 125°<br>(benzene) | 1770 | 5.68 (q) | 1.57 (d) | 7.3 (m) | $C_{18}H_{13}ClN_2O_2$<br>(324.8) |
| **5d** | 3 | 81 | 167°<br>(benzene) | 1765 | | 1.4–2.1 (m) | 8.03 (s) | $C_{16}H_{15}ClN_2O_2$<br>(302.8) |
| **6a** | 4 | 21 | 76°<br>(*n*-hexane) | 1775 | | 5.38 (d)[f] | 8.63 (t)[f] | $C_5H_3NO_3$<br>(125.1) |
| **6b** | 4 | 33 | 157°<br>(benzene) | 1785 | | 5.46 (s) | 7.6 (m) | $C_{11}H_7NO_3$<br>(201.2) |
| **6c** | 4 | 45 | 153°<br>(benzene) | 1775 | 5.81 (q) | 1.77 (d) | 7.6 (m) | $C_{12}H_9NO_3$<br>(215.2) |
| **6d** | 4 | 57 | 115°<br>(benzene) | 1770 | | 1.4–2.1 (m) | 8.62 (s) | $C_{10}H_{11}NO_3$<br>(193.2) |

[a] Uncorrected.
[b] At 60 MHz with TMS as the internal standard.
[c] The elemental analysis (C, H, N) were in good agreement with the calculated values.
[d] Mass spectrum: $m/e = 236$ ($M^+ + 2$, 31%), 234 ($M^+$, 100%), 205 (18%), 155 (20%), 138 (36%), 111 (38%).
[e] Sublimation in vacuo at 180–200°/0.1 torr.
[f] $J \approx 1$ Hz.

**Preparation of 2-Alkynyl 2-Chloro-(4-chlorophenylhydrazono)acetates (3); General Procedure:**

A cold aqueous solution of 4-chlorobenzenediazonium chloride (15 mmol) is added dropwise to a stirred solution of **2** (15 mmol) and sodium acetate (30 mmol) in 70% aqueous methanol (60 ml), under ice-cooling. The mixture is stirred overnight at room temperature. The solid material is isolated by filtration and recrystallized from ethanol to give **3**. See Table 2.

**Preparation of 2-Alkynyl Chlorooximinoacetates (4); General Procedure:**

Isoamyl nitrite (30 mmol) is added dropwise to a stirred solution of **2** (25 mmol) in diethyl ether saturated with hydrogen chloride (50 ml). The mixture is allowed to stand at room temperature for 8 h, the solvent and volatile compounds are then removed in vacuo at 60–70° bath temperature. The oily residue is dissolved in pentane/dichloromethane (4:1) and kept in the refrigerator overnight. In the case of **2a, b, d**, this procedure leads to crystalline **4a, b, d**. No crystals were obtained in the case of **2c**, compound **4c** was obtained only as a crude oil. See Table 2.

**Preparation of 6-Oxo-2,6-dihydro-4*H*-furo[3,4-*c*]pyrazoles (5); General Procedure:**

A solution of compound **3** (10 mmol) and triethylamine (50 mmol) in dry benzene (1000 ml) is refluxed until all the starting hydrazone is consumed (T.L.C.). After cooling, the mixture is washed to neutrality with dilute hydrochloric acid and dried with sodium sulfate. The solvent is removed and diisopropyl ether is added to the residue. Filtration gives practically pure **5** (N.M.R. analysis). Analytically pure samples are obtained by recrystallization from an appropriate solvent. See Table 3.

**Preparation of 6-Oxo-4*H*,6*H*-furo[3,4-*c*][1,2]oxazoles (6); General Procedure:**

A solution of triethylamine (20 mmol) in dry benzene (100 ml) is added, during 2 h, to a boiling solution of compound **4** (10 mmol) in dry benzene (900 ml). The mixture is refluxed for 2 h, then allowed to cool, washed with dilute hydrochloric acid up to neutrality, dried with sodium sulfate, and evaporated under reduced pressure. When starting from **4b–d**, treatment of the oily residue with diisopropyl ether causes separation of solid material, which affords pure **6b–d** upon recrystallization from benzene. In the case of **4a**, the residue is chromatographed on a silica gel column (60 g, benzene/ethyl acetate 9:1 as eluent) to give **6a**. See Table 3.

Received: June 23, 1975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