1,1,1-Trichloro-4,4-diethoxy-3-buten-2-one and its Trichloroacetylacetate Derivatives: Synthesis and Applications in Regiospecific Preparation of Azoles


Núcleo de Química de Heterociclos (NUQUIMHE), Departamento de Química, Universidade Federal de Santa Maria, 97105-900 Santa Maria, RS, Brazil
Fax +55(55)2208031; E-mail: mmartins@base.ufsm.br
Received 15 May 2003; revised 21 July 2003

Abstract: The synthesis of 1,1,1-trichloro-4,4-diethoxy-3-buten-2-one and three trichloroacetylacetate derivatives from the acylation reaction of respective trialkyl orthoacetates and orthopropionates with trichloroacetyl chloride in good yields, is reported. The title compounds were used for the regiospecific preparation of two isoxazoles and five pyrazoles in the cyclocondensation with hydroxylamine and hydrazines, respectively. The transformation of the trichloromethyl group under mild conditions into carboxylic groups is also described.

Key words: isoxazoles, pyrazoles, 4,4-diethoxy-3-buten-2-one, alkyl trichloroacetylacetates

Pyrazoles and isoxazoles have a long history of applications in the pharmaceutical and agrochemical industry. Especially, pyrazoles containing polyfluoroalkyl groups are of considerable interest due to their herbicidal, fungicidal, insecticidal, analgesic, antipyretic and anti-inflammatory properties.1 In addition, isoxazoles are reported to possess various types of biological activities.2 The pyrazoles-3(5)-ethyl esters and derivatives thereof are known to be important intermediates in the preparation of agrochemicals, microbicides, herbicides, plant growth regulators and protectants.5

The main synthetic method to prepare pyrazoles and isoxazoles involve the [3+2] cyclization such as the classical β-diketone with hydrazines,4–6 and with hydroxylamine,7 respectively. In pyrazole synthesis, most of these reactions give two isomers (3- and 5-trihalomethylpyrazoles) and/or hydroxypyrazolines.5

In recent years, we have developed general syntheses of 1,1,1-trihalo-4-methoxy-3-alken-2-ones,7,8 an important halogen-containing building block, and their usefulness in heterocyclic preparations, e.g., isoxazoles7,9,10 pyrazoles,6,11 pyrazolium chlorides,12 pyrrolidinones,13 pyrimidines,14 pyridines,15 thiazines16 and diazepines,17 have been described. These compounds have been also used as precursors for the synthesis of (5)-ethoxy-carbonylpyrazoles18 and 5-ethoxy-carbonylisoxazoles19 in a one-pot procedure.

Although Hojo et al.20 have already reported the synthesis of trihaloacetylketene acetals by trichloroacylation of triethyl orthoacetate, there is a lack of systematic synthesis and applications of these substrates in the literature. Thus, as a part of our research program, we have developed a systematic preparation of 1,1,1-trihalo-4,4-dialkyl-3-buten-2-one (or haloacetylketene dialkyl O,O-acetals) and explored their usefulness in heterocyclic synthesis. The aim of this work is to report a simple and efficient method to obtain 1,1,1-trichloro-4,4-diethyl-3-buten-2-one (2a) and its not yet reported trichloroacetylacetate derivatives 3a–c, (Scheme 1). Also, this work shows the applications of 2 and 3 in the synthesis of some isoxazole and pyrazole derivatives (Scheme 2).

It has been reported20 that the reaction of triethyl orthoacetate with trichloroacetyl chloride in carbon tetrachloride and basic media at room temperature, leads to 1,1,1-trichloro-4,4-diethyl-3-buten-2-one (2a) in good yield. In this work, using a slightly modified procedure, alkyl trichloroacetyleclacetates 3a–c were prepared from the reaction of 1a–c with trichloroacetyl chloride in diethyl ether in the presence of pyridine at room temperature (Scheme 1).

Cyclization reaction of 2a with hydrazines and hydroxylamine gave 3-trichloromethyl-3-ethoxy-pyrazoles 4a,b and 3-ethoxy-5-trichloromethyl-4,5-dihydroisoxazole 6a, regiospecifically (Scheme 2).
Treatment of 3a (or 3b) with hydrazine (methyl- or phenylhydrazine) hydrochloride in ethanol under reflux furnished 3-ethoxycarbonyl-5-hydroxypyrazoles 7a–c, with simultaneous transformation of trichloromethyl group into carboxyl group.18,19 Treatment of 3a (or 3b) with hydroxylamine hydrochloride in water and pyridine at room temperature gave the 3-hydroxy-5-trichloromethyl-4,5-dihydroisoxazole 8a (Scheme 2). Compound 8a can be dehydrated in sulfuric acid to afford the corresponding 3-hydroxy-5-trichloromethylisoxazole, as described elsewhere.7

According to the methodology developed in our laboratory18,19 to obtain carboxyalkylisoxazoles and carboxyalkylpyrazoles from the trichloromethylazoles, we performed the synthesis of compound 5a from the compound 4a in good yield. The reaction was performed in 20% HCl at 40 °C, under stirring for 12 hours (Scheme 3).

The disadvantages of the published21 method over the present one to obtain 5 and 7 are: (i) the methods are limited to the synthesis of one compound, or (ii) they involve several steps for the synthesis, or (iii) they use precursors that are not readily available.

The regiospecific synthesis of novel 5-trichloromethyl-3-ethoxy-1-phenyl-1H-pyrazole (4d), from the cyclocondensation reaction of 2a with phenyl hydrazine was carried out in a molar ratio of 1:1 using carbon tetrachloride as solvent (Scheme 4).

However, the 4,5-dihydropyrazole intermediate 4c is unstable in carbon tetrachloride, and hence was not isolated, but it was possible to prove the structure of 4c by 1H NMR spectroscopy when the reaction was carried out in a NMR tube.22 From our previous results, it was observed that, in general, the 5-trihalomethyl-5-hydroxy-4,5-dihydroisoxazoles6,11 are dehydrated easily than the corresponding 4,5-dihydroisoxazoles.7,9,10 This fact is probably due to the larger electron-donating effect of the nitrogen (N-1) in pyrazoles than the oxygen (O-1) in isoxazoles. This trend is confirmed by the fact that when the N-1 of pyrazole bears an electron-withdrawing substituent, the stability of its hydrated form increases.6,11

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers without further purification.1H, 13C, and 2-D NMR spectra were recorded on a Bruker DPX 400 spectrometer (1H at 400.13 MHz and 13C at 100.63 MHz) at 298 K, digital resolution of ±0.01 ppm, 0.5 M in CDCl3 containing TMS as internal standard. All spectra were recorded in 5 mm tubes, at natural abundance. The assignment the N-methyl groups of 4b and 7a was based on two-dimensional correlation spectrum HMBC (Heteronuclear Multiple Bond Correlation) with the coupling constant optimized to 7 Hz. (three bond 13C-1H coupling constants).

Mass spectra were recorded in a HP 5973 MSD connected to a HP 6890 GC and interfaced by a Pentium PC. The CG was equipped with a split-splitless, injector, auto sampler, cross-linked HP-5 capillary column (30 m 0.32 mm of internal diameter), and helium was used as the carrier gas.

1,1,1-Trichloro-4,4-diethyl-3-buten-2-one (2a)
To a stirred solution of triethyl orthoacetate (1b; 4.87 g, 30.0 mmol) and pyridine (5.22 g, 66.0 mmol) in CCl4 (30 mL) was added dropwise, with cooling, trichloroacetyl chloride (10.91 g, 60 mmol) in CCl4 (30 mL), and the mixture was stirred at r.t. for 1 d. The mixture was washed with 10% ice-cold aq Na2CO3 solution (50 mL), then with H2O (2 × 50 mL), and dried (MgSO4). The solvent and pyridine
were removed under reduced pressure, and the residue was distilled under reduced pressure (30 °C/2 mbar) to give 2a as an oil in satisfactory purity (Table 1).

**Alkyl Trichloroacetylacetates 3a–c; General Procedure**

To a stirred solution of trichloroacetyl chloride (10.91 g, 60 mmol) in Et₂O (30 mL) kept at 0 °C, were added dropwise the respective triethyl orthoacetate or orthopropionate (60 mmol), and pyridine (30 mmol) in Et₂O (30 mL). The mixture was stirred for 16 h at r.t. (25–30 °C) and then washed with 0.1 N HCl (20 mL) and H₂O (3 × 20 mL). The organic layer was dried (MgSO₄), the solvent was removed by rotary evaporator, and the product was purified by distillation (Table 1).

**3-Ethoxy-5-trichloromethyl-4,5-dihydroisoxazole (6a)**

A solution of hydroxylamine hydrochloride (0.15 g, 2.2 mmol) in H₂O (10 mL) was added to a stirred solution of 2a (0.52 g, 2 mmol) in pyridine (0.17 g, 2.2 mmol) at r.t. The mixture was stirred over-

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Selected Physical Constants, NMR Spectra Data and Yield of Compounds 2–8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product</td>
<td>Yield* (%)</td>
</tr>
<tr>
<td>2a</td>
<td>82</td>
</tr>
<tr>
<td>3a</td>
<td>90</td>
</tr>
<tr>
<td>3b</td>
<td>91</td>
</tr>
<tr>
<td>3c</td>
<td>95</td>
</tr>
<tr>
<td>4a</td>
<td>60</td>
</tr>
<tr>
<td>4b</td>
<td>61</td>
</tr>
<tr>
<td>4d</td>
<td>77</td>
</tr>
<tr>
<td>5a</td>
<td>95</td>
</tr>
<tr>
<td>6a</td>
<td>71</td>
</tr>
<tr>
<td>7a</td>
<td>75</td>
</tr>
<tr>
<td>7b</td>
<td>75</td>
</tr>
<tr>
<td>7c</td>
<td>91</td>
</tr>
<tr>
<td>8a</td>
<td>85</td>
</tr>
</tbody>
</table>
night at r.t. The solvent was evaporated in a rotary evaporator and the residue was extracted with CHCl₃ (15 mL). The organic layer was washed with H₂O (3 × 15 mL), dried (MgSO₄), and the solvent was removed in a rotary evaporator to afford the product in satisfactory purity (Table 1).

3-Hydroxy-5-trichloromethyl-4,5-dihydroisoxazole (8a)
A solution of hydroxylamine hydrochloride (0.15 g, 2.2 mmol) in H₂O (10 mL) was added to a stirred solution of 3a or 3b (2 mmol) in pyridine (0.17 g, 2.2 mmol) at r.t. The mixture was stirred for 24 h at 30 °C. The solvent was evaporated in a rotary evaporator and the residue was extracted with EtO (15 mL). The organic layer was washed with 0.5 N HCl and H₂O (2 × 10 mL), the organic layer was dried (MgSO₄), and the solvent was removed by rotary evaporator. The product obtained was purified by recrystallization from hexane–EtOHAc (1:1) (Table 1).

3-Trichloromethyl-5-ethoxy-1H-pyrazoles 4a,b
A CCl₄ solution of 2a (0.52 g, 2 mmol) was added dropwise to a cooled stirred solution (at 0 °C) of anhyd hydrazine or methylhydrazine (2.2 mmol). The reaction mixture was stirred for 12 h at r.t. After this time, H₂O (10 mL) was added and the organic phase was extracted with CHCl₃ (15 mL). The organic layer was washed with 0.5 N HCl and H₂O (2 × 10 mL), the organic layer was dried (MgSO₄), and the solvent was removed by rotary evaporator. The residue was purified by column chromatography (Merck silica gel 230–400 mesh) using hexane–CHCl₃ (8:2) as eluent (Table 1).

3-Ethoxy-1H-pyrazole-5-carboxylic Acid (5a)
A 20% solution HCl (10 mL) was added to 4a (0.46 g, 2 mmol) and the mixture was stirred at 40 °C for 12 h. The solvent was evaporated and the crude product was kept under vacuum. The product was isolated with satisfactory purity (Table 1).

3-Ethoxycarboxyl-5-hydroxy-1H-pyrazoles 7a–c
Compound 3a or 3b (2 mmol) was added to a stirred solution of hydrazine (methyl- or phenylhydrazine) hydrochloride (2.2 mmol) in EtOH (15 mL) at r.t. The mixture was refluxed for 24 h. The solvent was evaporated and to the residue was added H₂O (10 mL) and the organic phase was extracted with CH₂Cl₂ (15 mL). The organic layer was washed with dry MeOH (1 × 15 mL), dried (MgSO₄) and the solvent was removed under reduced pressure. The residue was purified by column chromatography (Merck silica gel 230–400 mesh) using hexane–CHCl₃ (8:2) as eluent (Table 1).

Acknowledgment
The authors thank the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq/PADCT-II/FINEP, and Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS) for financial support. Fellowships from CNPq, CAPES and FAPERGS are also acknowledged.

References


(22) 4c: 1H NMR: δ = 1.36 (t, 3 H, CH₃), 4.20 (q, 2 H, CH₂), 3.25 (d, 1 H, J = 18 Hz, H₄), 3.70 (d, 1 H, J = 18 Hz, H₃). For 1H and 13C NMR data of 2a and 4d, see Table 1.