Monatshefte für Chemie 116, 551—556 (1985)

Monatshefte für Chemie
Chemical Monthly

Nitriles in Organic Synthesis: The Reaction of Trichloroacetonitrile with Active Methylene Reagents

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(Received 28 February 1984. Revised 2 September 1984. Accepted 3 October 1984)

The reaction of trichloroacetonitrile with active methylene reagents such as acetylacetone, benzoylacetone, cyanoacetamide and cyanoacethydrazide is reported. A new simple route for the synthesis of polysubstituted phenols, pyrazoles and pyrroles is also described.

(Keywords: Polysubstituted phenols; Pyrazoles; Pyrroles)

Nitrile bei organischen Synthesen: Die Reaktion von Trichloracetonitril mit aktiven Methylen-Reagentien

Es wird über die Reaktionen von Trichloracetonitril mit aktiven Methylen-Reagentien wie Acetylaceton, Benzoylaceton, Cyanacetamid und Cyanacethydrazid berichtet. Ein neuer einfacher Weg für die Synthese polysubstituierter Phenole, Pyrazole und Pyrrole wird beschrieben.

Introduction

Activated nitriles are highly reactive reagents that have found extensive application in organic synthesis[1—3]. In the last decade we have reported several novel syntheses of heterocycles utilising activated nitriles as starting materials[4—8]. Although trichloroacetonitrile has an exceptionally reactive cyanofunction, with exception of our previous reports[9—12], its utility in heterocyclic synthesis has received very little attention[13]. In conjunction to previous work, we report here on the reactivity of this reagent toward a variety of active methylene reagents with the aim of preparing new, otherwise not readily obtainable, cyclic compounds.

Results and Discussion

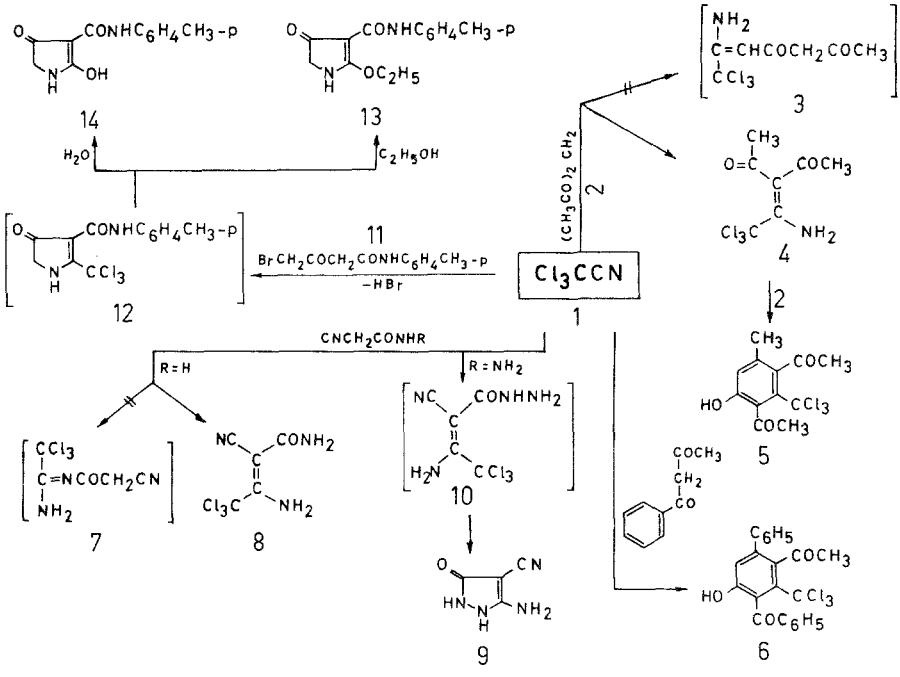
It has been found that trichloroacetonitrile (**1**) reacts with acetylacetone (**2**) to yield a 1:1 adduct. Two theoretically possible structures were considered (cf. structure **3** and **4**). Structure **3** was readily ruled out based on ^{1}H NMR data which revealed two almost identical methyl signals at 2.2 ppm; no methylene protons CH_2 were detectable. When compound **4** was treated with another molecule of **2** the phenol derivative **5** was obtained. Compound **5** can be assumed to be formed via condensation of the active methylene of **2** with **4** through elimination of ammonia with a subsequent cyclisation accompanied by loss of a water molecule. The formation of **5** may be considered as a new simple route for the synthesis of polyfunctionally substituted phenols.

Benzoylacetone reacted with **1**, to yield directly the phenol derivative **6**. Trials to isolate an acyclic intermediate of this reaction were unsuccessful.

Similar to the ready addition of **1** to β-diketones, compound **1** also afforded a 1:1 adduct on treatment with cyanoacetamide. Again two isomeric structures may be considered for the adduct (cf. structures **7** and **8**). Structure **7** could be readily eliminated based on spectral data and chemical evidence. Thus, the reaction product **8** revealed absence of signals for active methylene protons and proved to be stable under conditions expected to effect ready cyclisation of **7**.

The contrast to the behaviour of **1** towards cyanoacetamide, cyanoacethydrazide reacted readily with **1** to yield 5-amino-4-cyanopyrazolone (**9**). The formation of this product is assumed to proceed via initial *Michael* addition of the active methylene of cyanoacethydrazide to the cyano group of **1** to afford the acyclic intermediate **10** which then readily cyclizes with the loss of chloroform. A similar nucleophilic substitution of the trichloromethyl group has been recently described and discussed[11]. Attempts to separate any acyclic intermediates for this reaction were unsuccessful. It affords a novel, interesting synthesis of compound **9**.

Compound **1** reacted with γ-bromoacetylaceto-*p*-toluidide (**11**) to yield a product, the structure of which was found to be dependent on the applied reaction conditions. Thus, when **1** and **11** were left in ethanolic sodium acetate overnight, the ethoxypyrrolone derivative **13** was obtained. On the other hand, treatment of **1** with **11** in refluxing ethanol (95%), in presence of triethylamine, followed by treatment with water, gave the hydroxypyrrolone derivative **14**. **13** and **14** are suggested to be formed via initial *Michael* addition followed by loosing hydrogen bromide giving the pyrrolone derivative **12** which then reacts with ethanol or water to yield the final isolable products with elimination of chloroform in both



cases. Ready replacement of trichloromethyl group with ethanol or water under mild conditions has been recently observed by us. Compounds **13** and **14** are potentially tautomeric and several tautomers can exist. Spectral data indicate the presence of more than one tautomer in equilibrium in solid state and in solutions. In solid state these compounds are found in the keto form (see formula scheme) since the IR shows a carbonyl absorption ($\sim 1\,680\,cm^{-1}$) (KBr pellets); in solution however, these compounds are found in the enol form (3-hydroxypyrrole structure), as evident from the presence of an OH signal in the NMR spectrum.

Experimental

All melting points are uncorrected. IR spectra were recorded on a Beckman spectrophotometer and ^1H NMR on a Varian EM-390-90 MHz spectrometer. The microanalysis were performed by the microanalytical unit at Cairo University.

1,1-Diacetyl-2-amino-2-trichloromethylethylene (**4**)

Trichloroacetonitrile (0.01 mol) was treated with acetylacetone (0.01 mol) in 50 ml ethanol in the presence of sodium acetate (0.01 mol). The reaction mixture

was left overnight, triturated with water and the product so formed was collected by filtration and crystallized from ethanol, m.p. 58 °C (colourless) yield 70%.

IR: 3 350 and 3 190 (NH_2), 1 660 (conjugated C=O); 1 610 (C=C).

^{1}H NMR: 6.0 (s, 2 H, NH_2), 2.2 (s, 6 H, methyl protons).

$C_7H_8NO_2Cl_3$ (244.5). Found C 34.1 H 3.0 N 5.3 Cl 43.1.
Calcd. C 34.3 H 3.2 N 5.7 Cl 43.5.

2,4-Diacetyl-3-trichloromethyl-5-methylphenol (**5**)

Equimolecular amounts of **4** (0.01 mol) and acetylacetone (0.01 mol) in dry toluene (30 ml) were refluxed for 3 h in the presence of triethylamine (0.1 ml). Toluene was evaporated *in vacuo* and the reaction product was crystallized from methyl alcohol; m.p. 95 °C (buff, darkens when exposed to air); yield 60%.

IR: 3 500 (phenolic OH), 1 680 (conjugated C=O), 1 620 (C=C).

^{1}H NMR: 2.2 (s, 3 H, CH_3 protons), 2.4 (s, 6 H, two CH_3CO), 6.9 (s, 1 H, OH), 7.3 (s, 1 H-aromatic proton).

$C_{12}H_{11}O_3Cl_3$ (309.5). Found C 46.3 H 3.2 Cl 34.1.
Calcd. C 46.5 H 3.5 Cl 34.4.

2-Benzoyl-3-trichloromethyl-4-acetyl-5-phenylphenol (**6**)

To a mixture of **1** (0.01 mol) and benzoylacetone (0.01 mol), in 30 ml dry toluene, triethylamine (0.1 ml) was added. The reaction mixture was refluxed for 3 h. Toluene was evaporated *in vacuo*. The product was crystallized from methanol; m.p. 148 °C (buff, darkens on standing); yield 55%.

IR: 3 480 (phenolic OH), 1 705–1 680 (conjugated C=O).

^{1}H NMR: 2.3 (s, 3 H, methyl protons), 7.3–7.9 (two multiplets, 12 H, aromatic protons and OH).

2-Cyano-3-amino-4-trichloromethylcrotonamide (**8**)

Trichloroacetonitrile (0.01 mol) was treated with cyanoacetamide (0.01 mol) in ethanol (50 ml) in presence of sodium acetate (0.01 mol). The reaction mixture was left overnight and then triturated with water. The solid product so formed was collected by filtration and crystallized from ethanol; m.p. 152 °C (yellow); yield 65%.

IR: 3 400 and 3 350 (free NH_2), 3 350 and 3 300 (amide NH_2), 2 200 (CN), 1 680 (C=O).

$C_5H_4N_3OCl_3$ (328.5). Found C 26.3 H 1.4 N 12.4 Cl 32.1.
Calcd. C 26.2 H 1.2 N 12.7 Cl 32.4.

5-Amino-4-cyanopyrazolone (**9**)

Trichloroacetonitrile (0.01 mol) reacted overnight with cyanoacethydrazide (0.01 mol) in ethanol (50 ml) in presence of sodium acetate (0.01 mol). The reaction mixture was treated with water and the solid product so formed was collected by filtration and crystallized from *DMF*; m.p. > 300 °C (brown); yield (75%).

IR: 3 400 and 3 320 (NH_2), 3 100 (NH), 2 200 (CN), 1 700 (ring C=O) and 1 660 (C=N).

$C_4H_4N_4O$ (124). Found C 38.5 H 3.0 N 44.9.
Calcd. C 38.7 H 3.2 N 45.1.

Formation of compound **13**

Trichloroacetonitrile (0.01 mol) was treated with 0.01 mol of **11** in 50 ml of ethanol in the presence of sodium acetate (0.01 mol). The reaction mixture was left overnight, treated with water and the solid product so formed was collected by filtration and crystallized from *DMF*; m.p. > 300 °C (brown); yield 60%.

IR: 3250 and 3000 (NH), 1720 (side chain C=O), 1680 (ring C=O), 1660 (C=N and δ NH).

^{1}H NMR: 1.25 (s, 1H, OH), 1.65–2.3 (m, 7H, NH of the side chain and methyl protons), 3.3 (q, 2H, CH_2), 6.8–7.8 (m, 6H, aromatic protons and pyrrole NH).

$C_{14}H_{16}N_2O_3$ (260). Found C 64.3 H 5.9 N 10.5.
Calcd. C 64.6 H 6.1 N 10.7.

Formation of compound **14**

Equimolecular amounts of **1** (0.01 mol) and **11** (0.01 mol) were refluxed in 30 ml of ethanol (95%) in the presence of triethylamine (0.1 ml) for 3 h. The reaction mixture was poured on ice-cold water. The solid product so formed was collected by filtration and crystallized from ethanol; m.p. > 300 °C (brown); yield 70%.

IR: 3450 (OH), 3300 (NH), 1700 (side chain C=O), 1680 (ring C=O) and 1650 (C=N and δ NH).

^{1}H NMR: 1.3 (s, 1H, free OH), 2.3 (s, 4H, NH of the side chain and methyl protons), 4.6 (br. s, 1H, H-bonded OH), 6.8–7.6 (m, 6H, aromatic protons and pyrrole NH).

$C_{12}H_{12}N_2O_3$ (232). Found C 62.3 H 5.3 N 12.3.
Calcd. C 62.0 H 5.1 N 12.5.

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Verleger: Springer-Verlag KG, Mölkerbastei 5, A-1010 Wien. — Herausgeber: Österreichische Akademie der Wissenschaften, Dr.-Ignaz-Seipel-Platz 2, A-1010 Wien, und Gesellschaft Österreichischer Chemiker, Eschenbachgasse 9, A-1010 Wien. — Redaktion: Währinger Straße 38, A-1090 Wien. — Hersteller: Adolf Holzhausens Nachfolger, Kandlgasse 19-21, A-1070 Wien. — Verlagsort: Wien. — Herstellungsort: Wien. — Printed in Austria.