Vilsmeier-Haack preparation of 2-acylpyrroles using bis(trichloromethyl)carbonate and \(N,N\)-dimethylacylamines

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A series of 2-acylpyrroles were synthesized by using bis(trichloromethyl)carbonate and \(N,N\)-dimethylacylamines as Vilsmeier-Haack reagents under mild conditions in good yields.

2-Acylpyrrole derivatives are a kind of compounds which exhibit antipyretic, analgesic, antiinflammatory and other pharmacological actions\(^1\)-\(^3\). There are many methods to synthesize 2-acylpyrrole, for example, Vilsmeier-Haack reaction, Oddo reaction and Frödel-Crafts reaction et al.\(^4\)-\(^6\). Among these, Vilsmeier-Haack reaction is the most convenient one owing to its simple, mild condition and good yield. The traditional Vilsmeier-Haack reagents involve a combination of phosphorus oxychloride or phosgene and \(N,N\)-dimethylacylamine\(^7\)-\(^15\). In this paper we report a new method for the introduction of a \(\alpha\)-keto-function into pyrroles by means of bis(trichloromethyl)carbonate (BTC) and \(N,N\)-dimethylacylamines as Vilsmeier-Haack reagents (Scheme 1) instead of phosphorus oxychloride and toxic phosgene, to provide an alternative route for the synthesis of 2-acylpyrroles.

BTC is a useful auxiliary to prepare intermediates for the synthesis of many specific organic compounds\(^16\). Increasing reports, especially patents, have appeared on its use as a synthetic tool for a variety of purposes since reintroduction by Eckert et al.\(^16\)(b). It may be used instead of phosgene, phosphorus oxychloride and thionyl chloride in reactions with many nucleophiles. Reactions with BTC usually proceed under mild conditions and often afford good yields. Moreover, BTC is safe to handle and convenient to store and transport because it is a stable solid. In this paper, we describe the availability of BTC as one part of Vilsmeier-Haack reagent.

Our experiments show that the acylation of pyrroles can be conveniently carried out by using BTC and \(N,N\)-dimethylacylamines as Vilsmeier-Haack reagents in carbon tetrachloride. In this system a series of 2-acylpyrroles were synthesized under mild conditions in good yields. The results were summarized in Table I. In comparison to other reported methods for the preparation of 2-acylpyrroles, the major advantages of our procedure are its simplicity, the low cost, and environmentally compatible reagent employed. Although theoretically, \(1/3\) mole of BTC and one mole of \(N,N\)-dimethylacylamine as one mole of Vilsmeier

Mechanism of Vilsmeier-Haack reaction using POCl\(_3\) as reagent has been extensively studied\(^17\). The key of electrophilic substitution depends on the formation of the active
intermediates, chloromethyleneiminium salt. We think that possible mechanism of the chloromethyleneiminium salt (1) formation using BTC and N,N-dimethylacylamines as Vilsmeier-Haack reagents is as follow (Scheme 2). (1) attacks suitable carbon nucleophile of the pyrrole ring and hydrolyze to produce corresponding 2-acylpyrroles (Scheme 3).

![Scheme 3](image)

As for acylation of pyrrole, it was found sequence of addition influenced obviously the yield of product in our experiment. The pyrrole should be added after the active intermediate was formed by reacting BTC with N,N-dimethylacylamine at the mole rate 1:3. If the pyrrole was added at the beginning of the reaction, the yield would decrease to 70% or so. The reason is that pyrrole can react with BTC to form side-product (Scheme 4).\(^{(a)}\)

![Scheme 4](image)

Our experiments also show that the reaction temperature is very important since at ≥60°C, the reaction mixture will be black and difficult to process.

In summary, acylation of pyrroles using BTC (instead of phosphorus oxychloride) and N,N-dimethylacylamines as Vilsmeier-Haack reagents, is a viable process which avoids the formation of phosphorous salt and thus will be advantageous in industrial applications from the standpoint of safety and environmental acceptability.

**Experimental**

Melting points were obtained with a capillary melting point apparatus and were uncorrected. Infrared spectra were recorded on a Thermo Nicolet Avatar 370 spectrophotometer. \(^1\)H NMR spectra (CDCl\(_3\)) on a Varian Mercur plus-400 spectrometer using TMS as internal standard. N,N-Dimethylacylamines was synthesized according to literature.\(^{(a)}\) Organic solvents were obtained from commercial sources. Preparative TLC separations were carried out with silica gel GF-245 coated glass plates.

**Typical procedure for synthesis of 2-acylpyrrole:** A solution of BTC (0.733 mmol) in carbon tetrachloride (7 mL) was slowly added to a solution of N,N-dimethylacetamide (2.2 mmol) in carbon tetrachloride (5 mL) at 0°C over a period of 15 min. The mixture was allowed to stir for 15–30 min. Then pyrrole (2 mmol) was added and the mixture was heated to 40–50°C for 1 h and poured into ice water. 2 N Sodium hydroxide was added to the solution and the mixture was extracted with ether (10 mL x 3). The combined organic phase was washed with water, brine in turns and dried over anhydrous sodium sulfate, the solvents were removed under reduced pressure. The obtained residue was subjected to chromatographic purification on TLC silica gel to give 2-acylpyrrole (2a) in 90% yield. The characterization and spectral data of the products are as follows:

| Compd. | R\(_1\) | R\(_2\) | Yield (%)\(^b\) |
|-------|-------|-------|-----------------|
| 2a    | H     | CH\(_3\) | 90              |
| 2b    | H     | CH\(_2\)CH\(_3\) | 87              |
| 2c    | H     | C\(_6\)H\(_5\) | 85              |
| 2d    | H     | p-CH\(_3\)C\(_6\)H\(_4\) | 86              |
| 2e    | CH\(_3\) | CH\(_3\) | 92              |
| 2f    | CH\(_3\) | CH\(_2\)CH\(_3\) | 88              |
| 2g    | CH\(_3\) | C\(_6\)H\(_5\) | 84              |
| 2h    | CH\(_3\) | p-CH\(_3\)C\(_6\)H\(_4\) | 85              |

\(^{(a)}\)Substrate (2 mmol), N,N-dimethylacrylamine (2.2 mmol), BTC (0.733 mmol) and CCl\(_4\) (12 mL) were used.

\(^{b}\)Yields based on substrates.
1.6 Hz, 4.0 Hz, ArH), 6.79 (1H, t, J 2.2 Hz, ArH), 6.11 (1H, dd, J 2.4 Hz, 4.0 Hz, ArH), 3.94 (3H, s, NCH3), 2.79 (2H, q, J 7.4 Hz, CH2). 1.16 (3H, t, J 7.4 Hz, ArH), 3.94 (3H, s, NCH3), 2.79 (2H, q, J 7.4 Hz, CH2). 1.16 (3H, t, J 7.4 Hz, ArH), 3.94 (3H, s, NCH3), 2.79 (2H, q, J 7.4 Hz, CH2). 1.16 (3H, t, J 7.4 Hz, ArH), 3.94 (3H, s, NCH3), 2.79 (2H, q, J 7.4 Hz, CH2).

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