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(Chloro-phenylthio-methylene)dimethylammonium chloride (CPMA): a new coupling reagent for the formation of ester and amide bond

Laurent Gomez,[a] Silvère Ngouela,[a] Françoise Gellibert,[b] Alain Wagner[a,*] and Charles Mioskowski[a,*]

[a]*Faculte de Pharmacie, Laboratoire de Synthèse Bioorganique, Universite Louis Pasteur de Strasbourg, UMR 7514 associée au CNRS, 74 route du Rhin, 67401 Illkirch, France*

[b]*Laboratoire GlaxoWellcome, Centre de Recherches, 25, Avenue du Québec, 91951 Les Ullis Cedex, France*

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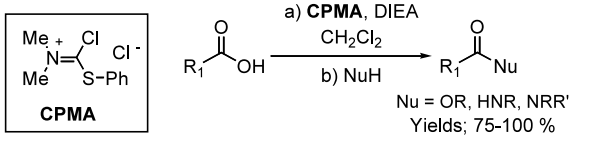
Abstract—CPMA is an efficient agent for the formation of esters and amides from carboxylic acids. It is compatible with substrates that are sensitive to basic conditions or oxophilic reagents. The reaction proceeds without racemization of chirally labile carboxylic acids. All these advantages make CPMA a valuable adjunct to the existing arsenal of coupling reagents. © 2002 Elsevier Science Ltd. All rights reserved.

Ester and amide bond formation belongs to the most important and frequently used reactions in organic synthesis.[1] These reactions are well known and extensively documented. They usually rely on the formation of an activated ester that undergoes nucleophilic substitution. Several reagents are described to form a wide variety of activated intermediates like Palomo's reagent,[2] Castro's reagent,[3] carbodiimides derivatives,[4] and Mukayama's reagent[5] as well as the more recent DEPBT[6] and Taddei's reagent.[7] Although very useful, efficient and complementary, they show to some extent drawbacks like formation of side products difficult to remove, low solubility, chemo-selectivity or reactivity problems.

In an earlier paper, we described the synthesis of (chloro-phenylthio-methylene)dimethylammonium chloride (CPMA) and its use for the selective chlorination of primary hydroxyl groups.[8] Herein, we wish to report the use of CPMA for the formation of ester and amide bonds by coupling a carboxylic acid and an alcohol or an amine respectively under mild reaction conditions (Scheme 1).

We first attempted to form the ester bond by slow addition of CPMA to a mixture of carboxylic acid and alcohol (Scheme 2). It afforded after 6 hours at room temperature the desired ester and chloroalkane in a 3/2 ratio according to ^{1}H NMR analysis. Similarly, addition of a primary alcohol to a mixture of CPMA and the carboxylic acid afforded a mixture of the desired ester and chloroalkane as side product. Finally we found that addition of alcohol to a mixture of CPMA, DIEA and carboxylic acid gave exclusively the ester.

Reaction of the carboxylic acid and CPMA affords an activated intermediate **A**. In the presence of HCl the formation of **A** is equilibrated, and both CPMA and **A** coexist in the media. Tertiary amines trap the HCl, hence shift the equilibrium toward the exclusive formation of **A**. When the coupling reaction is carried out without base, the alcohol reacts both with the intermediate **A** and with CPMA. A mixture of the desired ester and the chloroalkane is thus obtained. In the presence of a base, since only **A** exists in the medium, addition of a primary alcohol affords exclusively the desired ester



Scheme 1. Structure of CPMA and its use as a coupling reagent.

Keywords: coupling reagent; ester bond; amide bond; methylene ammonium salt.

* Corresponding authors. Tel.: 33 3 90 24 42 95; fax: 33 3 90 24 43 06; e-mail: alwag@aspirine.u-strasbg.fr; mioskowski@bioorga.u-strasbg.fr

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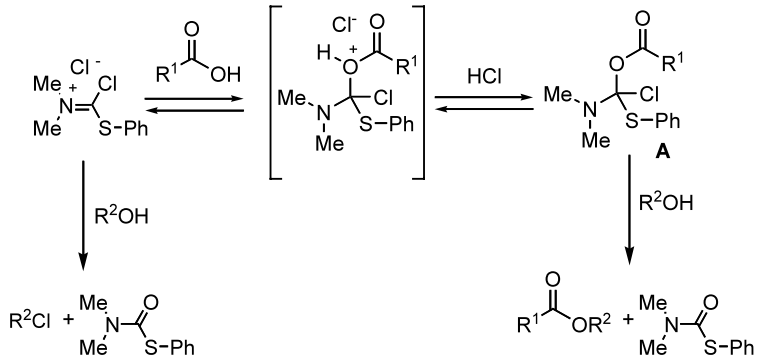
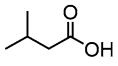
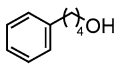
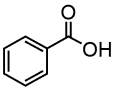
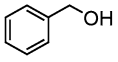
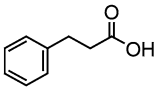
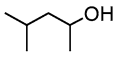
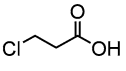
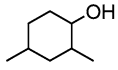
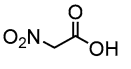
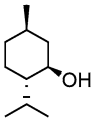
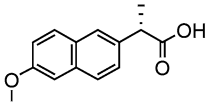
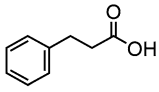
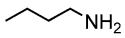
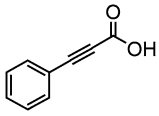


Scheme 2. Reactivity of CPMA in the presence of a carboxylic acid and an alcohol.

Table 1. Synthesis of various esters and amides

Entry	Acid	Nucleophile	Isolated Yield (%)
1			94[a]
2			82[a]
3			93[b]
4			100[b]
5			91[b]
6			75[b]
7			100[b]
8			100[b]

a) CPMA, DIEA, CH_2Cl_2, b) CPMA CH_2Cl_2

with concomitant formation of thiocarbamate as side product. Noteworthy, the thiocarbamate is recovered quantitatively at the end of the reaction. As no thiophenol is formed, no unpleasant odour is noticed. Among the different bases tested (DBU, NEt_3, K_2CO_3) we found that Hunig's base (DIEA) was superior for this process.

Further coupling reactions were performed by addition of CPMA (1.3 equiv.) to a solution of carboxylic acid (1.0 equiv.) and DIEA (1.1 equiv.) in anhydrous dichloromethane (0.3 M) under argon at 0°C. After 30 min the alcohol (1.0 equiv.) is added. The resulting solution is stirred at rt for 12 h. The reaction is then quenched by addition of saturated aqueous ammonium chloride. The aqueous layer is extracted with dichloromethane and the combined organic layers are dried over magnesium sulfate and concentrated under vacuum. The residue is purified by silica gel column chromatography. Various alcohols, amines and acids

were subjected to this procedure; the obtained results are summarized in Table 1.

Coupling reactions were successfully carried out with primary, secondary and crowded alcohols (entries 1–6). Moreover, since CPMA does not react with secondary alcohols, addition of DIEA is not necessary when bulky substrates are involved.

It is to be noted that the mildness of this novel reagent enables performance of coupling reactions on sensitive substrates. For instance, β-cloropropionic acid, that readily undergoes a β-elimination reaction under mild basic conditions,[9] quantitatively yielded the desired ester (entry 4). Also, nitroacetic acid that usually gives complex mixture of products upon treatment with oxophilic reagents,[10] led under our conditions the corresponding ester in 91% yield (entry 5).

We also showed that CPMA do not cause the racemization of a chirally labile carboxylic acid. Indeed, coupling of enantiomerically pure carboxylic acid and alcohol (entry 6) gave the corresponding ester in 75% isolated yield. ^{1}H NMR analysis of the crude mixture did not evidence any epimerization.

Interestingly, the reaction did not proceed with tertiary alcohols. The activated intermediate seems not to be reactive enough to undergo nucleophilic attack from a crowded alcohol. This is consistent with our previous statement that a primary alcohol react selectively with CPMA in the presence of a secondary one.[8] Thus the somewhat lower yield in entry 6 is probably explained by the steric hindrance of both the acid and the alcohol.

The reaction was then extended to the formation of amide bonds. Addition of 2 equiv. of primary and secondary amine to a mixture of carboxylic acid and CPMA, quantitatively yield the amides (entries 7, 8).

As reported CPMA is prepared by reaction of *S*-phenyl-*N*,*N*′-dimethyl dithiocarbamate with phosgene.[8] In our precedent paper we overestimated the stability of CPMA toward humidity. Indeed, when preparing the salt we noticed the formation of a variable amount of *N*,*N*′-dimethyl phenylcarbamate arising form CPMA hydrolysis. To avoid the formation of this side product we advise to filter and wash the white solid (CPMA) under argon, or alternatively to remove the solvent under inert atmosphere with a syringe (a typical procedure is given below).

In summary CPMA is an efficient reagent for the formation of esters or amides by coupling carboxylic acids and alcohols or amines, respectively. CPMA proved to be compatible with substrates that are sensitive to basic conditions or to oxophilic reagents. Moreover it was shown that the reaction proceeds without epimerization of chirally labile carboxylic acid. All these advantages make CPMA a valuable adjunct to the existing arsenal of coupling reagents.

Typical procedures:

Preparation of CPMA: A solution of phosgene in toluene (1.9 M, 1.78 mL, 3.4 mmol) is added drop-wise at 0°C to a solution of *S*-phenyl-*N*,*N*′-dimethyl dithiocarbamate (591 mg, 3 mmol) in methylene chloride (3 mL). After stirring at rt for 1.5 h, CPMA is precipitated by addition of ether (3 mL). After 5 min the solvent is syringed out and the resulting solid is washed two times by addition of anhydrous ether (10 mL) and removing by syringe. Finally CPMA (680 mg, 96%) is dried under vacuum and stored under argon.

Coupling reaction: A solution of the alcohol (1.0 mmol) in methylene chloride (1 mL) is added dropwise at 0°C to a solution of CPMA (307 mg, 1.3 mmol), carboxylic acid (1.0 mmol) and DIEA (1.1 mmol) in methylene chloride (2.5 mL). The reaction is monitored by TLC and typically left overnight. The ester is then recovered by classical work up and silica-gel chromatography.

Acknowledgements

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