INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

SYNTHESIS OF AMIDES BY ACTIVATION OF CARBOXYLIC ACIDS USING PHOSPHONITRILIC CHLORIDE

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ARTICLE INFO

Article history
Received 25/01/2020
Available online
10/02/2020

Keywords
Phosphonitrilic Chloride,
Amides,
Carboxylic Acids.

ABSTRACT

A practical and efficient method has developed for the amidation of carboxylic acids using phosphonitrilic chloride trimer (PNT). We identified PNT for these transformations as an effective one pot procedure. The method is suitable alternative to traditional amidation. A variety of useful amides were prepared. Aromatic as well as aliphatic carboxylic acids have been reacted converted into corresponding amides in excellent yields.

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*Please cite this article in press as **Jitendra S. Pulle** et al. Synthesis of Amides by Activation of Carboxylic Acids Using Phosphonitrilic Chloride. Indo American Journal of Pharmaceutical Research.2020:10(01).*

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INTRODUCTION

One of the most important and commonly occurring functional group is amide present in many natural products. Generally, amides are the nitrogen containing carbonyl compound in which the functional group consisting of an acyl group is attached to the nitrogen atom. Amides have been extensively used as intermediates for the preparation of other functional groups such as amines, ketones and acids.

Due to the various applications, amides being important class of organic compounds [1-3] as pharmaceuticals [4] and agrochemicals.[5] Some of the amide derivatives possess biological properties such as anthelmintic, antihistamine, antifungal and antibacterial.[6–13] The amidation of carboxylic acid is an important reaction that is used in organic synthesis.[14-16] A key transformation is usually carried out by activating the carboxylic acid and their subsequent reaction with amines. Apart from the several protocols developed until now, there is still need for mild and efficient reagent which can be employed to activate the carboxylic acid having functional group compatibility. Thus a mild and suitable alternative procedure for amidation is always being demanded by chemical industries.

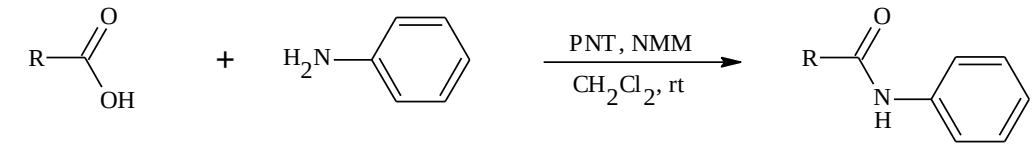
Traditionally, carboxylic acids were activated to acid chlorides in organic synthesis are generally prepared by the reaction of carboxylic acids with reagents such as thionyl chloride, oxalyl chloride, PCl_3, PCl_5 and several others.[17-19] In such a protocol, vigorous conditions are required and many of these reagents are highly corrosive and toxic, therefore unsuitable. Alternatively acid anhydrides were utilized instead of acid chlorides in amidation procedures. However in this method problem arises if the carboxylic acid is converted to a symmetric anhydride, 1 equivalent of carboxylic acid is lost as the byproduct of the amidation reaction. It requires additional processing for the isolation of acid and reconversion to anhydride and is an expensive. Use of mixed anhydride could be the solution to this problem but it gives a mixture of products.

Recently, a common approach involves treatment of the acid with a reagent to from an activated intermediate, which is then treated with an amine *in situ* to form the amide products. A few reagents were identified that allow coupling of carboxylic acids with amines. Rayle and Fellmeth [20] successfully used cyanuric chloride promoted amidation of carboxylic acid. Formation of peptide bond by means of 2-chloro-4,6-dimethoxy-1,3,5-triazine[21] was reported. 3,4,5-trifluorobenzene boronic acid,[22,23] N-Acylbenzotriazole, [24] Deoxo-Fluor,[25] Ph_3P/ trichloroisocyanuric acid, [26] fluorous 2- chloropyridinium hexafluorophosphate,[27] boric acid,[28] tin (II),[29] tosyl chloride,[30] phenyl silane,[31] TEP-4-DMAP, [32] Boron(III), [33] Borate esters, [34] Boric acid, [35] $TiCl_4$, [36] Acetylene or ethoxy acetylene, [37] were used for amidation of carboxylic acids. Amide bond formation was reported by using dithiocarbamate and DBU under microwave condition.[38]

Amides were synthesized by the coupling of carboxylic acids and azides via selenocarxylate and selenatriazoline.[39] The coupling reagents such as (4,5-Dichloro-6-oxo-6*H*-pyridazin-1-yl) phosphoric acid diethyl ester,[40] ionic liquids based on 1, 3-dialkylimidazolium and ammonium were used for the amidation of carboxylic acid with isocyanate.[41] Aryl amides were prepared by the reaction of carboxylic acids with isocyanates in methanol [42] and DMF.[43] These reagents are expensive and require an equivalent amount with respect to acids and separation of byproduct is difficult. Aldehydes were also underwent amidation reactions using reagents such as CuI/AgO_3,[44] oxone,[45] Lanthanide catalysts,[46] gold nanoparticles, [47]. Amides were also sythesised from alcohols and nitriles with complete atom economy [48].

Six membered cyclic ring containing three alternative P–N subunits with six chlorine atoms covalently bonded to phosphorous atom is called as phosphonitrilic chloride trimer (PNT). PNT is a white crystalline compound. It is thermally stable and soluble in variety of organic solvents. It shows more reactivity towards nucleophiles. [49] PNT has been used as acid activators for various organic transformations.[50-54]

Considering the applicability of amides, phosphonitrilic chloride (PNT) has been used as an efficient reagent for the amidation of carboxylic acids under mild conditions (Scheme 1). Aromatic as well as aliphatic carboxylic acids (I) have been reacted with aniline (II) in presence of PNT and NMM and converted into corresponding amides (III) in excellent yields.



R = Alkyl, Aryl

I II III

Scheme 1

Experimental

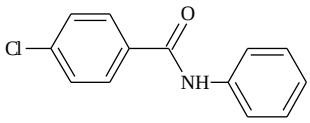
Experimental procedure

PNT (0.25 mmol) was dissolved in 10 ml dichloromethane and N-methyl morpholine (1.5 mmol) was added with constant stirring at temperature 0-5°C. After 30 minutes the respective carboxylic acid (1.5 mmol) was added and stirring was continued. After disappearance of carboxylic acid (TLC), aniline (1.4 mmol) was added and further stirring was continued at room temperature. The progress of the reaction was monitored by TLC (9:1; pet ether: ethyl acetate,v/v). After completion of reaction (2-3 hrs.), the reaction mixture was washed with 5 % $NaHCO_3$ (3×10 ml) followed by 2 N HCl (3×10 ml) and H_2O (2×10 ml). The organic layer was then dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure to get desired product. All products were purified by column chromatography.

Spectral analysis

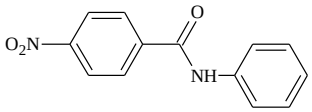
The formation of products were confirmed by comparison with authentic samples as well as by FTIR , ^{1}H NMR, ^{13}C and Mass spectroscopy. FTIR spectra were recorded on Thermo Nicolet Nexus 670 Spectrometer. (Resolution : 4 cm^{-1}), ^{1}H NMR and ^{13}C spectra were recorded with AVANCE 300 MHz NMR spectrometer in $CDCl_3$ + DMSO, mass spectra were recorded with GCMS.

4-Chloro benzalnilide (Entry 2)



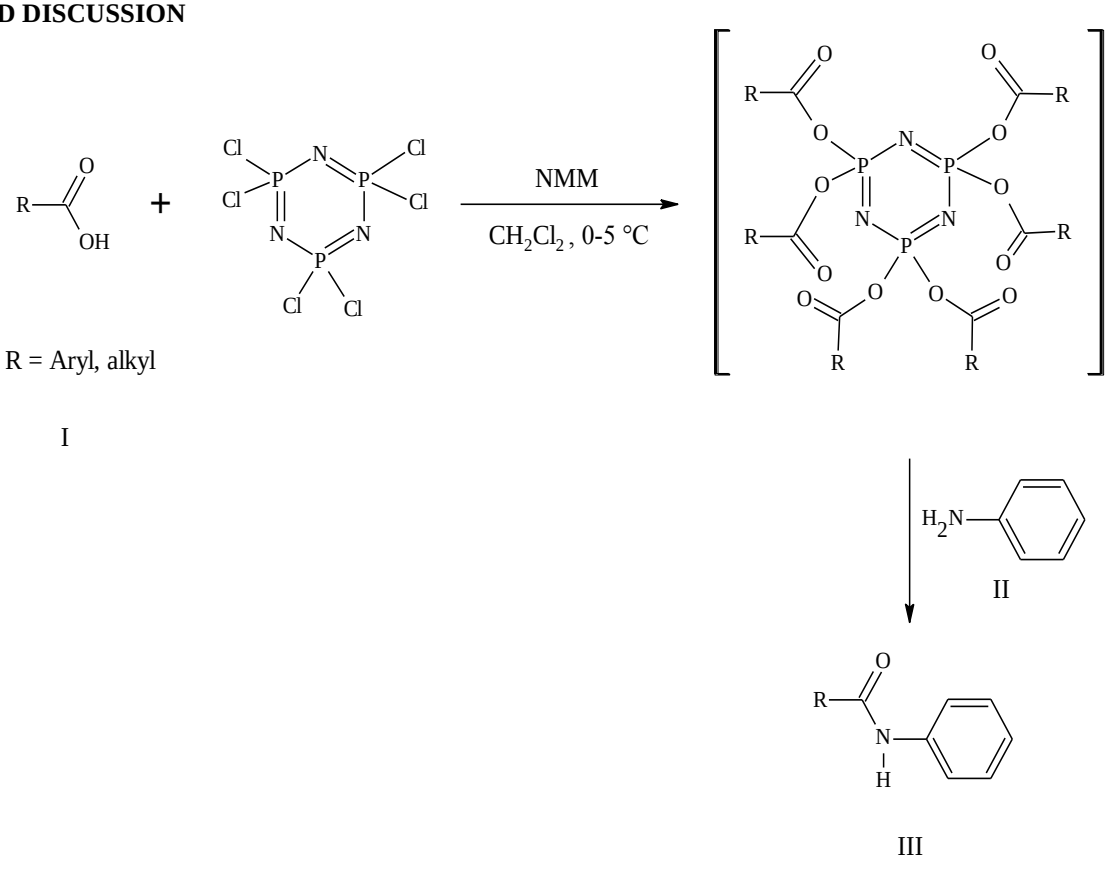
I R (KBr) cm^{-1} : 3349 (- NH -), 1653 (C=O)
^{1}H NMR (δ ppm) : 9.90(s, 1H, NH), 6.90–7.90 (m, 9H, Ar-H)
^{13}C NMR : 165 (>C=O), 136 (– C–Cl), 138 (–C–NH)
Mass : 231 (M^{+}, 28 %)

4-Nitro benzanilide (Entry 3)



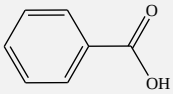
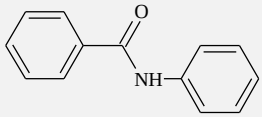
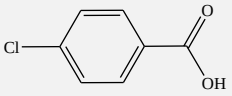
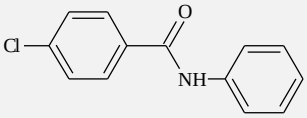
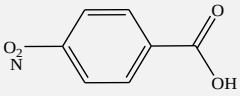
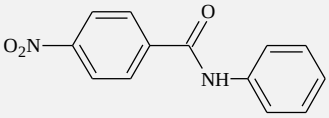
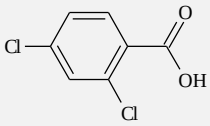
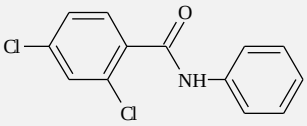
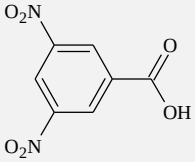
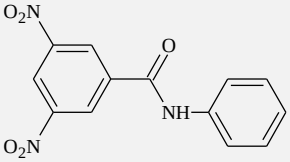
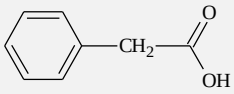
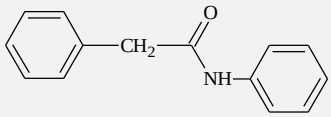
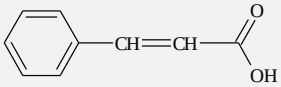
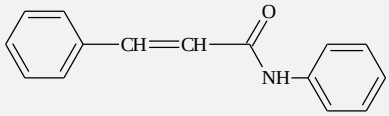
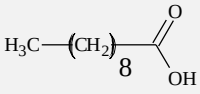
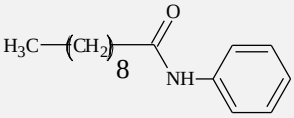
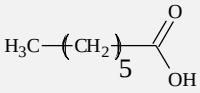
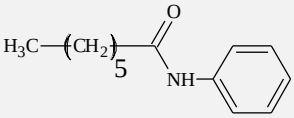
I R (KBr) cm^{-1} : 3320 (-NH-),1653 (C=O)
^{1}H NMR (δ ppm): 8.10 (s, 1H, NH); 7.00-8.20 (m, 9H, Ar–H)
^{13}C NMR : 164 (>C=O), 149 (–C–NO_2), 137 (–C–NH)
Mass : 242 (M^{+} 45 %)

RESULTS AND DISCUSSION



Scheme 2.

Table 1 : Synthesis of Amides Using PNT.

Entry	Acid	Amide	Time (hrs.)	Yield (%)
1			3	89
2			2.4	93
3			2	95
4			2.7	92
5			2.2	94
6			2.8	91
7			2.3	94
8			2.5	93
9			2.5	93

In the present work, phosphonitrilic chloride in combination with N-methyl morpholine (NMM) was used to activate 6 equivalent of carboxylic acid (I) and reacted with amine (II) to get corresponding amides (III) (Scheme 2) in excellent yield (Table 1). A variety of carboxylic acids were reacted with amines in presence of PNT as acid activator to afford corresponding amides in excellent yield under mild conditions. The method is applicable to both the aromatic as well as aliphatic carboxylic acids. The results show that the aromatic carboxylic acids with electron withdrawing substituents gave higher yields (Table 1, entries 2, 3, 4, 5).The aliphatic carboxylic acids also gave corresponding amides in excellent yields (entries 8, 9). The protocol is also useful for the conversion of unsaturated carboxylic acid to amide affording excellent yield of the product (entry 7). The method provides a clean route for generating amides with complete conversion within 2-3 hours (Table 1) compared to most coupling reagents which requires even reflux.

CONCLUSIONS

In conclusion, PNT acts as an excellent alternative activating agent for the amidation of carboxylic acid. The present protocol is a convenient and practical for the preparation of amides in excellent yields, offering significant improvement over the existing methodologies.

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