

Microwave-Assisted Clean Synthesis of Amides via Aza-Wittig Reaction under Solvent-Free Condition

*Murugan Sathishkumar, Sangaraiah Nagarajan, Poovan Shanmuga Velan,
Murugan Dinesh and Alagusundaram Ponnuswamy**

*Department of Organic Chemistry, School of Chemistry, Madurai Kamaraj University,
625-021 Tamilnadu, India*

O acoplamento de fosfazenos com cloretos de acila ou anidridos carboxílicos mediado por microondas na presença de fosfito de etila foi realizado, resultando nas correspondentes amidas, de maneira limpa e com bons rendimentos. Ao contrário das metodologias anteriores, que empregam solventes clorados, benzeno (cancerígeno), etc, este protocolo é eco-amigável, rápido e simples.

A solvent-free microwave-assisted coupling of phosphazenes with acyl chlorides or carboxylic anhydrides in presence of triethylphosphite has been accomplished resulting in a clean synthesis of amides in good yields. Unlike the prevailing time-consuming solution phase methodologies employing chlorinated solvents, benzene (carcinogenic), etc, the present protocol is an eco friendly, rapid and simple approach.

Keywords: microwave, solution phase, solvent-free, amide, aza-wittig

Introduction

Amide is an ubiquitous functionality prevalent in natural products, peptides and potential drugs.¹ In view of this, extensive research towards developing elegant protocols for amide bond formation is in progress wherein attempts are being continuously made to eradicate the difficulties and limitations enveloped with the prevailing methods.

Generally, the most relevant methodologies involve solution phase approach wherein the limitations associated with the polarity, refluxing temperature and the toxicity of the solvent/additives restrict their broad scope and question their eco-friendliness. Also, the components employed and formed as the by-products in the protocols play vital role in deciding the rate of the amide bond formation. Thus, all these aspects are to be considered in accomplishing time-conscious, eco-friendly protocols for amide bond formation.

In particular, the direct coupling of an amine with a carboxylic acid results in an acid-base reaction to form a

stable salt following which the amide bond formation has to fight against adverse thermodynamics as the equilibrium lies on the side of hydrolysis rather than synthesis (Scheme 1).

Herein, azeotropic removal of water accumulated in the solution has been attempted² for accomplishing an effective synthesis of amides. Alternatively, molecular sieves are added to the solution to trap the water and expedite the reaction.

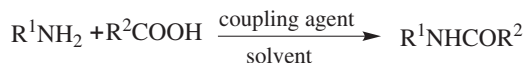
On the other hand, the direct coupling of amines with carboxylic acids has been assisted by coupling reagents³ (Scheme 2). Apparently, use of excess of coupling reagents and their corrosive nature is hazardous to the environment.

Further, other approaches like aminocarbonylation⁴ of aryl halides with amines and catalysis⁵ in amide bond formation in solvent medium are with limitations such as loading of metal carbonyls/catalyst for large scale preparation and difficulties in reactivation/reusability of deactivated catalyst which may preclude the scope of their applicability.



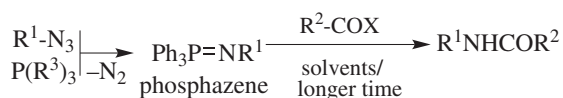
Scheme 1. Direct coupling of amines with carboxylic acids.

*e-mail: ramradkrish@yahoo.co.in



Scheme 2. Coupling of amines with carboxylic acids in presence of coupling agent.

An alternative solution phase protocol involves the coupling of Staudinger's phosphazenes,⁶ generated from phosphines and organic azides, with carboxylic acids⁷ (Scheme 3) or their derivatives⁸ to afford carboxamides. The limitations of this methodology are the usage of benzene (carcinogenic) or toluene as the solvent of choice, very long reaction times⁷ and solubility problems that arise with polar starting substrates.⁷



X = OH, Cl, OCOR

Scheme 3. Coupling of Staudinger's phosphazene with carboxylic acids or their derivatives.

The polarity of the substrates and reagents puts restriction to the number of useful solvents. Further, solvents employed may either enhance or retard the rate of the reaction performed in view of differing interactions. Above all, the above said preferred solvents restrict the possibility of exploring the effect of temperature on the rate of the amide bond formation. Sometimes, the reaction can not be studied at higher temperatures.

Results and Discussion

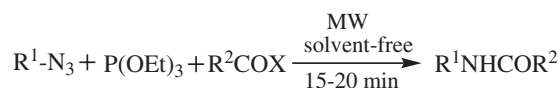
Microwave-assisted organic synthesis⁹ had replaced most of the time consuming conventional methodologies. Its applicability in amide bond formation has been scarcely studied. To the best of our knowledge, solvent-free coupling of phosphazenes with acid chlorides and anhydrides assisted by microwave has been never reported.

Hence, need for a better protocol avoiding the hazards to the environment becomes important. In this regard, we attempted the microwave-assisted aza-wittig coupling of the azides with acids in presence of triphenylphosphine under solvent-free condition. The reaction was fascinating in the sense, that the reaction was completed at 180 °C within 15 min with good yield of the amides. The above coupling in solvents have been reported⁷ and noted by us to afford the amides in 3-72 h. Thus the multifold increase in the rate under solvent-free condition has been apparently thought to be due to the close intimacy and collapsing of the reaction mixture. In spite of this advantage, the method

was still time consuming due to the need for the isolation of the by-product *viz.* triphenylphosphine oxide from the reaction mixture. This tempted us to simplify the protocol by some appropriate modifications.

This has been accomplished by substituting the acyl chlorides or the anhydrides in the place of the carboxylic acids and triethylphosphite in the place of triphenylphosphine. This would result in (i) enhancing the electrophilicity of the acyl carbon resulting in accelerating the reaction at relatively lower temperature and (ii) formation of water soluble triethylphosphate as the by-product. Based on these presumptions the present work was attempted, the findings of which are presented below.

In a typical procedure (Scheme 4), a mixture of triethylphosphite (1 mmol), organic azide (1 mmol) and acid anhydride/acid chloride (1.3 mmol) was irradiated with microwave for 15-20 min at the temperature indicated in Table 1 to afford the amide in good yield.



R¹ = primary, secondary, aryl

X = Cl or OCOR²

Scheme 4. Coupling of azides with carboxylic acid derivatives in the presence of triethyl phosphite.

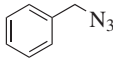

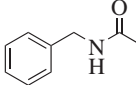
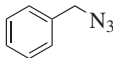
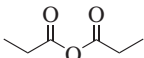
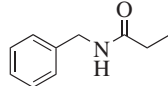
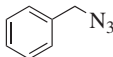
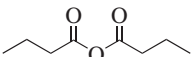
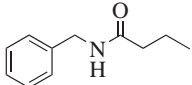
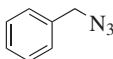

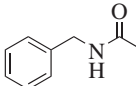
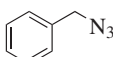
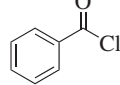
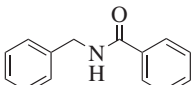


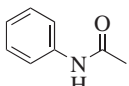

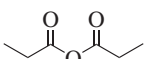
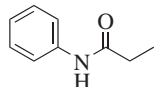

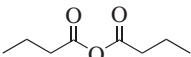
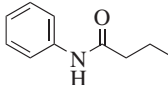


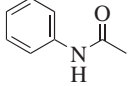

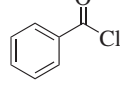
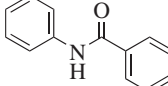
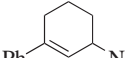

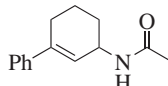
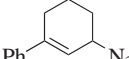
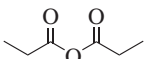
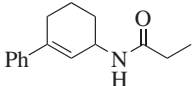
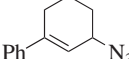
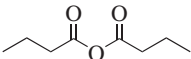
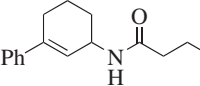
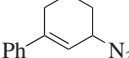

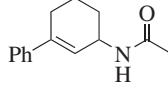
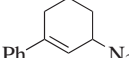
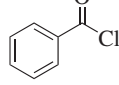
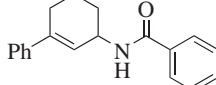
Conclusions

In conclusion, the present study reports a solvent-free microwave-assisted amide synthesis via coupling of phosphazenes with acyl chlorides or carboxylic anhydrides in presence of triethylphosphite. It is an eco-friendly, rapid and simple approach which avoids the limitations associated with time-consuming solution phase methodologies where benzene (carcinogenic), toluene and chlorinated solvents are preferably employed.

Experimental

All chemicals, reagents and solvents were of commercially high purity grade purchased from Avra Synthesis Pvt. Ltd. and Merck Ltd. India. Silica gel (60-120 mesh) was used for column chromatographic isolation and purification of the amides synthesized. Organic azides were prepared according to the literature procedures. Melting points were noted on electro-thermal apparatus and are uncorrected. ¹H NMR and ¹³C NMR spectra were recorded in CDCl₃ on Bruker Avance 300 MHz spectrometer and the chemical shifts are reported as δ values in parts *per million* (ppm)

Table 1. Microwave-assisted amide synthesis

entry	azides	acid chloride/anhydride	time / min	T / (°C)	amide	yield / (%)
1			15	100		74
2			15	100		78
3			15	100		84
4			15	100		71
5			15	100		76
6			20	100		75
7			20	100		80
8			20	100		83
9			20	100		70
10			20	100		77
11			15	150		81
12			15	150		85
13			15	150		88
14			15	150		77
15			15	150		79

^aisolated yield.

relative to tetramethylsilane, with *J* values in Hertz. The splitting patterns in ¹H NMR spectra are reported as follows: s = singlet; d = doublet; t = triplet; q = quartet; br s = broad singlet; br d = broad doublet; m = multiplet. ¹³C NMR data are reported with the solvent peak (CDCl₃ = 77.0) as the internal standard. Elemental analyses were performed by CNRS (Vernaison, Lyon) and were in agreement with the calculated values within ±0.4%. Spectral data of known amides are given in supplementary section.

General procedure for the microwave-assisted synthesis of amides (Table 1, entry 1-15)

To an intimate mixture of triethylphosphite (1 equiv.) and organic azide (1 equiv.) in a microwave vial (10 mL) equipped with a magnetic stirring bar, acid anhydride/acyl chloride (1.3 equiv.) was added in drops with stirring. Stirring was continued until liberation of nitrogen ceased and the reaction vessel was sealed with a septum. It was then placed into the cavity of a focused monomode microwave reactor (CEM Discover, benchmate) and operated for 15 min at 150 °C (temperature monitored by a built-in IR sensor). The reaction temperature was maintained by modulating the power level of the reactor. The reaction vessel was then cooled to room temperature and the residue was dissolved in ethyl acetate and washed repeatedly with water followed by saturated sodium bicarbonate solution to afford the amides as white solids.

N-(3-phenylcyclohex-2-enyl)acetamide (Table 1, entry 11)

Yield 195 mg (85%), mp 118 °C; IR (KBr) ν_{\max} /cm⁻¹: 3445 (–NH), 1671 (–C=O); ¹H NMR (300 MHz, CDCl₃) δ (ppm): 7.20-7.40 (m, 5H, ArH), 5.96 (pseudo triplet, 1H, C=CH), 5.60 (br d, 1H, *J* 7.5 Hz, –NH), 4.70 (br s, 1H, CHN), 1.99 (s, 3H, –COCH₃), 2.20-2.42 (m, 2H, alicyclic protons), 1.95-2.07 (m, 1H, alicyclic proton), 1.65-1.77 (m, 2H, alicyclic protons), 1.39-1.53 (m, 1H, alicyclic proton); ¹³C NMR (75 MHz, CDCl₃) δ (ppm): 169.4, 148.1, 139.9, 138.7, 126.2, 125.0, 123.6, 45.5, 29.0, 27.1, 23.2, 20.1. Anal. calc. (%) for C₁₄H₁₇NO: C, 78.10; H, 7.96; N, 6.51. Found (%): C, 78.25; H, 7.95; N, 6.51.

N-(3-phenylcyclohex-2-enyl)propionamide (Table 1, entry 12)

Yield 195 mg (85%), mp 97 °C; IR (KBr) ν_{\max} /cm⁻¹: 3444 (–NH), 1682 (–C=O); ¹H NMR (300 MHz, CDCl₃) δ (ppm): 7.20-7.50 (m, 5H, ArH), 5.96 (pseudo triplet, 1H, C=CH), 5.62 (br d, 1H, *J* 6.9 Hz, –NH), 4.70 (br s, 1H, CHN), 2.21 (q, 2H, *J* 7.5 Hz, COCH₂), 1.16 (t, 3H, *J* 7.5 Hz, –CH₃), 2.20-2.42 (m, 2H, alicyclic protons), 1.95-2.07 (m, 1H, alicyclic proton), 1.65-1.77 (m, 2H, alicyclic

protons), 1.39-1.53 (m, 1H, alicyclic proton); ¹³C NMR (75 MHz, CDCl₃) δ (ppm): 173.0, 141.2, 140.1, 128.2, 127.3, 125.1, 124.6, 45.3, 29.8, 29.1, 27.1, 20.3, 9.8. Anal. calc. for C₁₅H₁₉NO: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.46; H, 8.36; N, 6.10.

N-(3-phenylcyclohex-2-enyl)butyramide (Table 1, entry 13)

Yield 195 mg (85%), mp 128-129 °C; IR (KBr) ν_{\max} /cm⁻¹: 3447 (–NH), 1692 (–C=O); ¹H NMR (300 MHz, CDCl₃) δ (ppm): 7.25-7.39 (m, 5H, ArH), 5.96 (s, 1H, C=CH), 5.50 (br d, *J* 6.4 Hz, 1H, NH), 4.71 (br s, 1H, CHN), 2.36-2.40 (m, 2H), 2.16 (m, 2H), 1.95-1.97 (m, 1H, alicyclic protons), 1.81-1.83 (m, 2H, alicyclic protons), 1.68 (m, 2H, alicyclic protons), 1.55-1.57 (m, 1H, alicyclic protons), 0.95 (t, *J* 14.7 Hz, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃) δ (ppm): 172.9, 141.2, 140.2, 128.2, 127.3, 125.1, 124.6, 45.3, 29.8, 29.1, 27.2, 20.3, 18.3, 9.8. Anal. calc. for C₁₆H₂₁NO: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.88; H, 8.72; N, 5.77.

N-(3-phenylcyclohex-2-enyl)benzamide (Table 1, entry 15)

Yield 220 mg (79%), mp 154 °C; IR (KBr) ν_{\max} /cm⁻¹: 3451 (–NH), 1670 (–C=O); ¹H NMR (300 MHz, CDCl₃) δ (ppm): 7.29-7.75 (10H, m, ArH), 6.00 (br s, 1H, C=CH), 5.60 (br d, 1H, *J* 8.4 Hz, NH), 4.60 (br s, 1H, CHN), 2.20-2.42 (m, 2H, alicyclic protons), 1.95-2.07 (m, 1H, alicyclic proton), 1.65-1.77 (m, 2H, alicyclic protons), 1.39-1.53 (m, 1H, alicyclic proton); ¹³C NMR (75 MHz, CDCl₃) δ (ppm): 166.7, 148.2, 140.4, 138.6, 134.7, 131.3, 128.4, 126.9, 126.4, 125.1, 123.6, 45.0, 29.1, 27.2, 20.4. Anal. calc. for C₁₉H₁₉NO: C, 82.28; H, 6.90; N, 4.05. Found: C, 82.13; H, 6.91; N, 5.06.

Supplementary Information

The spectroscopic ¹H NMR, ¹³C NMR, IR data as well as the HRMS of selected compounds are available free of charge at <http://jbcs.sbq.org.br> as PDF file.

Acknowledgments

The authors, M. S, S. N and P. S acknowledge their grateful thanks to UGC for the sanction of UGC-JRF meritorious fellowship and IRHPA, DST for providing 300 MHz NMR instrument for recording the NMR spectra for the compounds synthesized.

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Submitted: May 31, 2011

Published online: September 1, 2011