One-pot sequential synthesis of isocyanates and urea derivatives via a microwave-assisted Staudinger-aza-Wittig reaction

One-pot sequential synthesis of Isocyanates and Ureas *via* the Microwave-assisted Staudinger aza-Wittig Reaction

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Abstract

A fast and efficient protocol for the synthesis of *N,N'*-disubstituted ureas from alkyl halides and primary or secondary amines has been developed. The synthetic pathway combines nucleophilic substitutions and a Staudinger-Aza-Wittig reaction in the presence of polymer-bound diphenylphosphine under 14 bar of CO_2 pressure and has been performed in a one-pot two-steps process. The protocol has been optimized under microwave irradiation and the scaling up experimented under conventional

condition in a Parr reactor. The final compounds were isolated after simple filtration in almost quantitative overall yields making this procedure facile and rapid to execute.

Keywords

Microwave-assisted reaction; Tandem Staudinger Aza-Wittig reaction; One-pot reaction; Isocyanates; Ureas.

Introduction

The industrial and commercial impact of isocyanates (R–NCO) is steadily growing; in particular, polyurethane output has led to a 5% yearly increase over the last decade.[1] Isocyanates play a relevant role as chemical intermediates in the manufacturing of thermoplastic foams, elastomers, adhesives, agrochemicals and pharmaceuticals The isocyanate group is also widely used as a precursor to several bioactive compounds and drugs that contain urea and carbamate moieties.[2]

Isocyanates were discovered by Wurtz in 1849,[3] and more than 20 methods for the preparation of R-NCO have now been listed and classified according to the reaction involved.[4, 5] The old procedure, that entails reactions between primary or secondary amines or amides with phosgene, is the most commonly used and described in papers [6, 7] and reviews.[8] The main drawbacks of this method are the extremely high toxicity of phosgene and the generation of a large amount of corrosive HCl. Moreover, the high temperature required by this process (> 250°C) makes the synthesis of lower molecular weight compounds impossible.

Apart from the catalytic carbonylation of nitro compounds, which is one of the most interesting alternatives for the synthesis of aromatic isocyanates, other alternative greener, non-phosgene routes to isocyanates have also been developed.[9] Of these,

the Curtius, Hoffman and Lossen rearrangements have quite often been used in the past and are still used for specific applications;[10-13] the Staudinger-aza-Wittig reactions have played a pivotal role in the construction of cyclic and acyclic compounds.[14-19] The replacement of phosgene by carbon dioxide (CO_2), which is nontoxic, abundant, and economical, is the principle advantage of this reaction. The mechanism of this transformation passes through iminophosphoranes which are a versatile intermediate that can react with CO_2 to generate isocyanates.[20] This reaction is compatible with a large number of functional groups and therefore has various uses in organic synthesis and can be exploited for the preparation of heterocyclic compounds. Isocyanate derivatives can generally be obtained in good yields, however it is necessary to avoid traditional triphenylphosphine to obtain high purity products.[21]

So called “enabling techniques”, mainly non-conventional energy sources such as microwaves (MW) and ultrasound (US), can dramatically enhance reaction rates in organic synthesis.[22,23] Kinetics and yields of any chemical modification are strongly improved by the optimal heat and mass transfer provided by dielectric heating and sonochemical conditions.[24-25] In general, MW in organic synthesis is a valid response to problems regarding long reaction time and high reagent excess. The use of dielectric heating to promote chemical reactions has become well established as a reliable technique which can be applied on a range of scales.[26] Despite MW irradiation being commonly used in organic synthesis, few publications describe this technique with gaseous reagents in closed vessel and in heterogeneous gas-phase reactions that are important for industrial processes.[27-31]

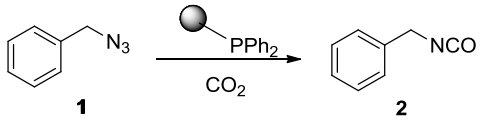
The aim of the present work is the development of new green and efficient synthetic procedures for easier access to isocyanates and urea libraries using a renewable carbon resource like CO_2. Since CO_2 requires a large energy input to be transformed,

[32] we have studied a synthetic procedure which uses a MW reactor (SynthWave by Milestone) which is well suited to parallel syntheses at any reaction temperature and gas pressure (up to 300°C and 200 bar). We aimed to successfully reduce reaction time and reagent excess, and to employ poorly reactive substrates and volatile, solid and supported reagents. In summary, we herein report an optimized protocol for MW-assisted Staudinger aza-Wittig reaction with polymer-bound diphenylphosphine (PS-PPh_2) in a CO_2 atmosphere. The study also aimed to prepare a series of symmetric and asymmetric alkyl/aryl urea compounds in a one-pot, sequential synthesis of urea derivatives from alkyl bromides. With the aim to verify the method feasibility under conventional heating, the protocol was experimented in a Parr reactor (90 mL), that could enable an easier scaling up..

Results and Discussion

The Staudinger aza-Wittig reaction is extremely versatile and can be used for the synthesis of many products. However, the by-product of this reaction is triphenylphosphine oxide which is difficult to remove. It is known that this reaction can be performed in a heterogeneous system using PS-PPh_2. Although the higher reagent cost, the use of PS-PPh_2 has the advantage of a much easier reaction workup.[33-38] A polymer regeneration procedure was described by Marsura *et al.*,[35] however a quasi stochiometric amount makes the recycling step not essential. With the aim to overcome costs limitations we recently described the preparation of triphenyl phosphine-loaded cross-liked cyclodextrin complexes as recyclable green catalyst.[39] The reactivity of polystyrene supported reagents strongly depends on the choice of solvent that can influence polymer swelling.[40] Solvent choice is therefore an important issue as it must allow the supported reagent to work in a friendly environment and, at the same time, facilitate the reaction outcome. In the first part of this work, we

have focused on the development of a MW promoted protocol for isocyanate synthesis with the aim of reducing reaction time and decreasing the amount of solid supported PS-PPh_2, which is usually added in large excess. The conversion of benzyl azide to benzyl isocyanate (Scheme 1) was selected as the model reaction and it was performed both under conventional conditions and under MW irradiation. Various solvents were compared at a number of temperatures thanks to the versatility of the SynthWave reactor (by Milestone) that handles multiple-sample racks. Experiments were performed at 90, 70 and 50°C at 14.5 bars of CO_2 pressure.



Scheme 1: Synthesis of benzyl isocyanate.

Table 1: Synthesis of benzyl isocyanate[a]

Entry	Solvent	Reaction condition	Conv.[b](%)	Yield[b](%)
1	Toluene	90°C, MW, CO_2 (14.5bar)	>99	75
2	Toluene	70°C, MW, CO_2 (14.5bar)	96	84
6	Toluene	50°C, MW, CO_2 (14.5bar)	82	78
3	THF	70°C, MW, CO_2 (14.5bar)	50	25
4	DMF	70°C, MW, CO_2 (14.5bar)	95	80
5	MeCN	70°C, MW, CO_2 (14.5bar)	>99	85
7	MeCN	50°C, MW, CO_2 (14.5bar)	>99	94
8[c]	MeCN	50 °C, CO_2 (1 bar)	41	25
9	MeCN	r.t, CO_2 (1 bar)	25 (95)[d]	21 (85)[d]
10[e]	MeCN	50 °C, CO_2 (14 bar)	93	89

[a] Unless otherwise stated, reactions were performed in the presence of PS-PPh_2 (5 eq)., reaction time 4h.
[b] Determined by GC-MS.
[c] The reaction was performed in an oil bath.
[d] Reaction time 24h.
[e] The reaction was performed in a Parr reactor.

As shown in Table 1, the reaction showed complete conversion when performed in toluene at 70°C as well as giving slightly higher compound purity when compared to

90°C. The conversion did not complete at 50°C. Conversion was low in THF and the isocyanate was present only as trace among side-products. MeCN, like toluene allowed higher conversion and yield to be achieved, even in comparison with DMF. In MeCN the conversion was still complete at 50°C in 4h. The influence of the CO_2 pressure on the reaction rate was evident by the poor conversion (40%) that was observed when the reaction was performed with 1 bar CO_2 at 50°C in an oil bath., In contrast the conversion reached 93% in a Parr reactor with 14 bar CO_2. At room temperature with 1 bar CO_2 the reaction occurs within 24 hours. The study was pursued in MeCN and toluene with the aim of optimizing the reaction conditions and a number of different reactions were performed at 50°C. As shown in Table 2, we confirm that the reaction was faster in MeCN than in toluene and that even full conversion was obtained after 1.5 h in many cases. An important goal was to reduce the PS-PPh_2 excess from 5 to 1.5 eq, with excellent results only in MeCN (Table 2) under MW irradiation. When the reaction was carried out in the Parr reactor, the highest conversion was 93% with 2 eq of PS-PPh_2.

Table 2: Synthesis of benzyl isocyanate[a].

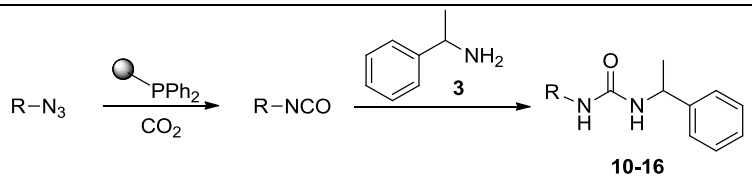
Entry	Solvent	PS-PPh_2 (eq.)	Time (h)	Conv.[b] (%)	Yield[b] (%)
1	Toluene	5	4	82	78
2	Toluene	5	2	71	71
3	Toluene	2	2	66	54
4	MeCN	5	4	>99	94
5	MeCN	5	2	>99	96
6	MeCN	5	1.5	>99	97
7	MeCN	5	1	80	76
8	MeCN	3	1.5	>99	97
9	MeCN	2	1.5	>99	95
10[c]	MeCN	2	1.5	93	88
11	MeCN	1.5	1.5	>99	98
12[c]	MeCN	1.5	1.5	88	82
13	MeCN	1	1.5	80	76

[a] Reactions were carried out in MW: **1**, PS-PPh_2, CO_2 (14.5 bar) 50°C.

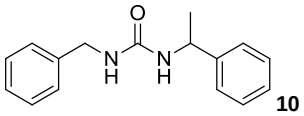
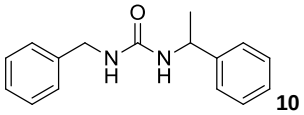
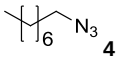
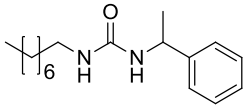
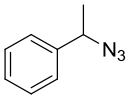
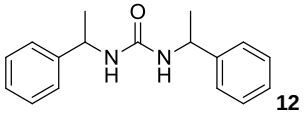
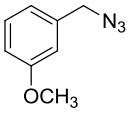
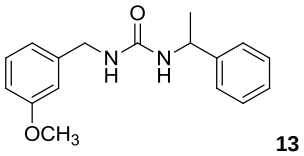
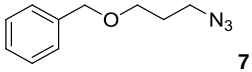
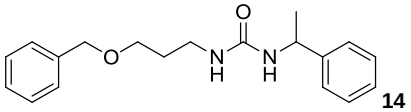
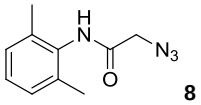
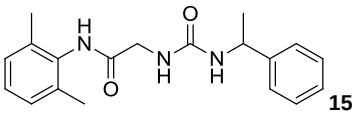
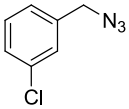
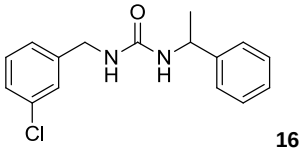
[b] Determined by GC-MS.
[c] Reactions were carried out in Parr reactor (90 mL): **1**, PS-PPh_2, CO_2 (14 bar) 50°C.

To confirm the versatility of our protocol, the method was extended to include a number of different substrates and the obtained isocyanates were also used for the synthesis of urea compounds via reaction with (±)-1-phenylethylamine **3** (see Scheme in Table 3). Seven different azido-derivatives were preliminarily synthesized from the alkyl halide and reacted *via* Staudinger aza-Wittig reactions. After the PS-PPh_3 was filtered, the isocyanate solution was directly subjected to an addition of 2 eq. of **3** and heated at 70°C in the MW reactor for 3h. Primary alkyl and benzyl azide derivatives were compared to secondary ones and the compatibility of the protocol towards different functional groups was also considered. The results obtained are given in Table 3 and show the yield of urea derivatives after purification from the amine excess using Dowex® 50WX8-200. The synthetic protocol is versatile and highly efficient with both primary and secondary azido derivatives as well as alkoxy and amido groups. The one-pot, two step procedure afforded urea derivatives in high yiled and purity via the isocyanate intermediate. To broaden the scope of the study the reaction was repeated in a bigger scale (80 mL) in a Parr reactor at the same pressure. Despite the good conversion, the purity of the product was slightly lower than that of the MW-assisted reaction.

Table 3: Synthesis optimization of urea derivatives.[a]



Entry	R-N_3	Product	Yield[b] (%)

1	**1**	 **10**	98
1[c]	**1**	 **10**	79
2	 **4**	 **11**	90
3	 **5**	 **12**	92
4	 **6**	 **13**	97
5	 **7**	 **14**	97
6	 **8**	 **15**	98
7	 **9**	 **16**	94

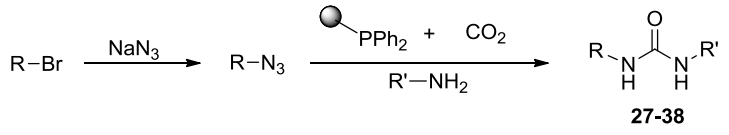
[a] Reactions were carried out in MW: azido derivative, PS-PPh_2 (1.5 eq.), CO_2 (14.5 bar) 50°C 1.5h, then **3** (2 eq.) 70°C 3h.
[b] Isolated yield.

To expand the scope of this method, a sequential one-pot synthesis from the alkyl bromide to the urea derivative was carried out without isolating the intermediates. The aim of this part of the work was the synthesis of the azido derivatives and their subsequent conversion to urea *via* the Staudinger aza-Wittig reaction and one-pot amine addition. The combination of reactants in a one-pot fashion can lead to

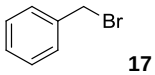
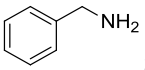
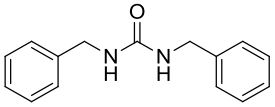
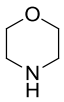
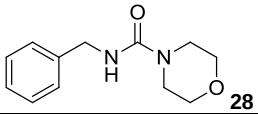
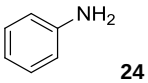
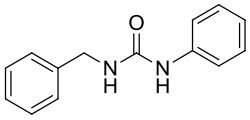
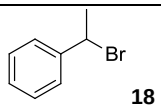
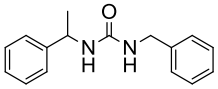
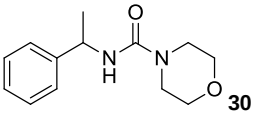
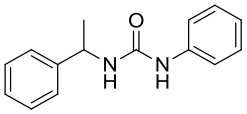
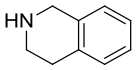
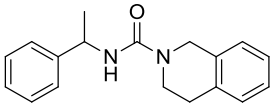
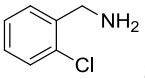
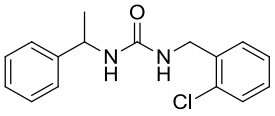
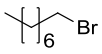
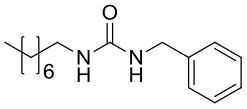
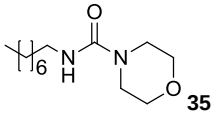
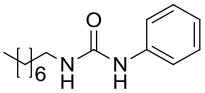
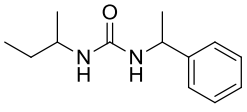
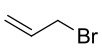
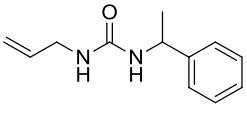
undesired side-product formation and, consequently, a lower yield. Therefore, the choice of the right solvent and reaction conditions if the key to the success of this transformation.

Our initial attempts focused on the synthesis of azido derivatives in MeCN. Generally performed in DMF, the S_N2 of alkyl bromide with NaN_3 can also be performed in MeCN. Even if NaN_3 is insoluble in MeCN at room temperature (< 0.005g/100 mL) its solubility increases at higher temperature. Furthermore, NaBr generated during the nucleophilic substitution is insoluble and can be removed by filtration as can the NaN_3 excess. These factors allow the work up procedure to be simplified and pure azido derivative solutions were obtained by filtration. Benzyl azide was successfully obtained from benzyl bromide after reaction in MW reactor at 95°C for 3h. After filtration, the benzyl azide solution was directly converted into urea by MW irradiation at 70°C for 3h in the presence of CO_2, PS-PPh_2 and benzylamine. The desired product was obtained in almost quantitative yields.

Table 4: One-pot MW promoted synthesis of a set of urea derivatives.[a]



27-38

Entry	R-Br	R-NH$_2$	Product	Yield[b] (%)
1	 **17**	 **22**	 **27**	98
2	**17**	 **23**	 **28**	98
3	**17**	 **24**	 **29**	98
4	 **18**	**22**	 **10**	97
5	**18**	**23**	 **30**	94
6	**18**	**24**	 **31**	98
7	**18**	 **25**	 **32**	98
8	**18**	 **26**	 **33**	98
9	 **19**	**22**	 **34**	89
10	**19**	**23**	 **35**	89
11	**19**	**24**	 **36**	88
12[c]	 **20**	**3**	 **37**	85
13[c]	 **21**	**3**	 **38**	83

[a] Reactions were carried out in MW: alkyl bromide, NaN_3 (2 eq.), MeCN, 95°C, 3h ; then PS-PPh_2 (1.5 eq), CO_2 (14.5 bar), amine (2 eq), at 50°C 1.5 h then 70°C 3h.
[b] Isolated yield.
[c] R-N_3 was synthesized in DMF and MeCN was then added.

The robustness of this MW promoted sequential one-pot procedure was established by synthesizing a set of 13 different ureas. A small set of five different primary and secondary alkyl and benzyl azides were synthesized. Besides azido derivatives **17-19**, two volatile azides **20** and **21** (*n*-butyl and allyl azide, respectively) were obtained under N_2 pressure. After filtration they were converted into urea. The procedure was performed in parallel and under 14.5 bar of CO_2 and even volatiles allyl and butyl azide reacted successfully. The results reported in Table 4 show that all final products were obtained in excellent to almost quantitative yield.

Conclusion

In conclusion, a MW-assisted, one-pot sequential protocol for the synthesis of urea derivatives from alkyl bromides has been described. This study has proven that in acetonitrile under high CO_2 pressure the Staudinger aza-Wittig reaction in presence of PS-PPh_2 is strongly promoted. Excellent results have been obtained under MW irradiation in a closed vessel also with gaseous reagents. The optimized procedure benefited from the use of the quasi-stoichiometric amount of PS-PPh_2 and can be applied for the efficient, safe, rapid and cost effective production of urea derivative libraries.

Experimental

All chemicals were purchased from Sigma-Aldrich (solvents from Carlo Erba SpA) and used without further purification. Solid diphenylphosphino-polystyrene (PS-PPh_2) was purchased from Novabiochem® (Cas-No: 39319-11-4, loading ≈ 1.2 mmol/g). Reactions were monitored by TLC on Merck 60 F254 (0.25 mm) plates, which were visualized by UV inspection and/or by heating after a spraying with 5% H_2SO_4 in ethanol or phosphomolybdic acid. MW-promoted reactions were carried out in a SynthWave (Milestone, Italy). NMR spectra were recorded on a Bruker Avance 300 (300 MHz and 75 MHz for ^1H and ^{13}C, respectively) at 25°C; chemical shifts were calibrated to the residual proton and carbon resonance of the solvents: $CDCl_3$ (δH= 7.26, δC = 77.16) or CD_3OD (δH= 3.31, δC= 49.00). GC-MS analyses were performed in a GC Agilent 6890 (Agilent Technologies - USA) that was fitted with a mass detector Agilent Network 5973, using a 30 m long capillary column, i.d of 0.25 mm and film thickness 0.25 µm. GC conditions were: injection split 1:20, injector temperature 250°C, detector temperature 280°C. Gas carrier: helium (1.2 mL/min), temperature program: from 70°C (2 min) to 300°C at 5°C/min. HRMS was determined using MALDI-TOF mass spectra (Bruker Ultraflex TOF mass spectrometer).

General Procedures

Representative procedure for alkyl isocyanate synthesis from alkyl azide: PS-PPh_2 (0.477 mmol) was added to a solution of alkyl azide (0.318 mmol) in MeCN (1.5 ml). The mixture was irradiated by MW for 1.5 h at 50°C (average power 70 W) under CO_2 (14.5 bar) and magnetic stirring. After the reaction, the mixture was filtered on a cartridge.

When performed in a Parr reactor PS-PPh_2 (6.36 mmol) was added to a solution of alkyl azide (3.18 mmol) in MeCN (80 ml). The solution was heated 2 h at 50°C under CO_2 (14.5 bar). After the reaction, the mixture was filtered on a cartridge.

Representative procedure for urea synthesis from alkyl isocyanate: The amine (0.636 mmol) was added to a solution of alkyl isocyanate (0.318 mmol) in MeCN (1.5 ml). The solution was irradiated by MW for 3 h at 70°C (average power 200 W) under N_2 (2 bar) and magnetic stirring. The solvent was then evaporated under vacuum, dissolved in MeOH and Dowex® 50WX8-200 was added. The mixture was stirred at r.t. for 15 min. The mixture was then filtered on paper and the solvent was evaporated under vacuum.

Representative "multi-pot" procedure for urea synthesis: NaN_3 (0.477 mmol) was added to a solution of alkyl bromide (0.318 mmol) in MeCN (1.5 ml). The mixture was irradiated by MW for 3 h at 95°C (average power 240 W) under N_2 (2 bar) and magnetic stirring. After the reaction, the mixture was cooled to r.t., filtered on paper, and PS-PPh_2 (0.477 mmol) and amine (0.636 mmol) were sequentially added. The mixture was irradiated by MW for 1.5 h at 50°C (average power 70 W) and 3 h at 70°C (average power 200 W) under CO_2 (14.5 bar) and magnetic stirring. Then, the mixture was filtered on a cartridge to remove the polymer-bound diphenylphosphinoxide. The solvent was then evaporated under vacuum, dissolved in MeOH and Dowex® 50WX8-200 was added. The mixture was stirred at r.t. for 15 min. Finally, the mixture was filtered on paper and the solvent was evaporated under vacuum.

When performed in a Parr reactor PS-PPh_2 (6.36 mmol) was added to a solution of alkyl azide (3.18 mmol) and amine (6.36 mmol) in MeCN (80 ml). The solution was heated 3 h at 70°C under CO_2 (14.5 bar). The mixture was filtered on a cartridge to remove the polymer-bound diphenylphosphinoxide and the residual polymer-bound

diphenylphosphine. The solvent was then evaporated under vacuum, dissolved in MeOH and Dowex® 50WX8-200 was added. The mixture was stirred at r.t. for 15 min. Finally, the mixture was filtered on paper and the solvent was evaporated under vacuum.

Supporting Information

File Name: Cravotto Supporting Information

Acknowledgements

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