Microwave-assisted selective and efficient synthesis of 1,3,5-triazinyl mono and bisureas

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ABSTRACT

An efficient and sustainable microwave-assisted approach for the one-step preparation of a wide range of 1,3,5-triazinyl mono- and bisureas has been developed, combining solvent-free conditions and microwave irradiation. In these conditions the very unreactive amino groups of 1,3,5-triazine-2,4-diamines successfully react with phenylisocyanate to yield selectively mono and bisureas.
This protocol resulted in the shortest reaction times reported so far and is generally applicable for the preparation of these valuable heterocyclic systems.

1. Introduction

Most biologically active natural products and synthetic compounds contain heterocyclic moieties in their structures.[1] They are known for their numerous pharmaceutical and medicinal applications and therefore, novel methods to synthesize such compounds are of major importance in the field of synthetic organic chemistry. Substituted 1,3,5-triazines are one of the most important and well known heterocycles with applications in several scientific fields, e.g., they are one of the classical heterocyclic compounds used in chemotherapy,[2] they are widely used in supramolecular chemistry because this remarkable heterocycle can be involved in all supramolecular interactions, coordination bonds, hydrogen bonding, electrostatic and charge-transfer attractions, and aromatic-stacking interactions.[3] Moreover, substituted triazines are well known for their excellent optoelectronic properties,[4] and they are used in supramolecular electronics.

The combination of urea moieties with hydrogen bonding donors[5] and a conjugated triazine core results in interesting building blocks with intriguing properties in crystal engineering and supramolecular polymers.[6] In addition, *N,N'*-disubstituted ureas have been used to synthesize crystalline solids with different architectures, ranging from one-dimensional chains and nanotubes, to two-dimensional sheets and three-dimensional frameworks.[7] Lastly, difunctional triazinyl mono- and bisureas possess very interesting self-assembly properties, which allows them to hierarchically arrange into supramolecular nanostructures as a result of non-covalent interactions in aqueous[8] or hydrophobic environments.[9] These unique properties have resulted in applications such as ambipolar thin film devices[10] and polyurea networks with 2D porous structures.[11]

Despite the importance and numerous applications of triazinylureas, synthetic methods for their preparation are limited. Previous synthetic strategies usually involve the alcoholysis of cyanoamino-*s*-triazines in the presence of hydrogen chloride.[12]

Since isocyanates are known to react with amides, the reaction between isocyanates and triazinylamines has been proposed as one of the main approaches for the synthesis of 1,3,5-triazinyl ureas. However, triazine amino groups are very unreactive since chemically act as amidines rather than amines and phenylisocyanate is also a low reactive isocyanate.

Described procedures are based on processes, which use hazardous solvents and harsh reaction conditions[13] and include the use or large excesses of more reactive alkyl isocyanates (up to 10-folds), reflux in solvents like pyridine and DMSO for large periods of time[14,15] and purification by column chromatography.[13,15,16] In

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many examples these reactions were applied to more reactive aminopyrimidines.

Other alternatives include the use of sodium hydride in THF,[17] or preparation in two steps by reaction of aminotriazines with phosgene or ethylchloroformiate and subsequent reaction with amines.[18]

Our research group has studied the reaction between amino s-triazines and different substrates like haloacetic acids, hydrazines, and aldehydes, resulting in unsuccessful reactions;[19] showing, in this sense, the poor nucleophilic character of the amino group coupled to the triazine ring.

Currently, new research avenues are focused on the development of sustainable synthetic routes[20] with short reaction times,[21] easy and fast purification, and atom economy. To this end, the application of non-conventional heating methods,[22] such as microwave irradiation,[23,24] or solvent-free processes,[25] can lead to a plethora of promising heterocyclic compounds and solve the problems of very unreactive compounds.[26]

As part of our on-going research toward the design of new heterocycles we describe a new way of synthesis, which makes possible to obtain s-triazinyl mono and bisureas, highlighting the environmentally benign and sustainable nature of the solvent-free (in most of the cases), microwave-assisted heterogeneous method and emphasizing the formation of self-complementary quadruple hydrogen-bonded arrays of the molecules obtained.

2. Results and discussion

Optimization of the synthetic protocol for the preparation of s-triazinyl mono and bisureas was performed by reacting 6-phenyl-1,3,5-triazine-2,4-diamine (**1a**) and phenylisocyanate (**2**) in solvent-free conditions under microwave irradiation and using different irradiation powers and temperatures (Table 1). The optimal **1a**/**2** ratio was found to be 1:2.1, reducing the excess of the isocyanate from 9, as previously described,[13] to 1.1 equiv. Interestingly, these conditions did not promote the formation of the bisurea **4a**, even using an excess of phenylisocyanate. Reducing the amount of **2** produced an incomplete reaction and traces of triazine **1a** were detected in the reaction crude (Table 1, entry 4). Only 30 min of reaction in solvent-free conditions were needed to obtain **3a** in 44% yield (Table 1, entry 1) but the yield did not improve upon further irradiation (Table 1, entry 3).

Table 1
Synthesis of [1,3,5]-triazinylmonourea (**3a**)

Entry[a]	Solvent[b]	P (W)	t (min)	T (°C)	Yield[c] (%)
1	—	25	30	105	44
2	—	CH	30	105	**3a**/**1a** 63:37[d]
3	—	25	60	105	45
4[e]	—	25	30	105	Traces of **1a**
5	DMSO	25	30	105	Complex mixture
6	Toluene	25	15	100	68
7	Toluene	CH	15	100	**3a**/**1a** 68:32[d]

[a] Phenylisocyanate (2.1 equiv).
[b] Solvent, 1 mL/mmol of **2**.
[c] Isolated yields.
[d] Not isolated. Ratio **1**/**3**, determined by ^{1}H NMR.
[e] Phenylisocyanate (1 equiv).

Formation of slurry in solvent-free conditions was thought to limit conversion. Therefore, we added small aliquots of solvent to homogenize the reaction. Addition of 1 mL of DMSO led to the

formation of a complex mixture of products, and monourea **3a** was obtained in low yield (Table 1, entry 5). The rapid heating inherent to this highly polar solvent justifies this result. In contrast, the use of toluene (1 mL/mmol of **2**) enables a better control over the reaction temperature and resulted in a 68% yield of **3a** in only 15 min (Table 1, entry 7). In a non-polar solvent, microwaves are directly absorbed by the substrates and the solvent homogenize the temperature. In consequence, in these conditions the advantages of microwave irradiation are more pronounced.[27]

Anhydrous solvents were required to prevent the formation of 1,2-diphenylurea that cannot be separated from the reaction product. Formation of this side product can be explained by the sequence of reactions shown in Scheme 1. Addition of water to phenylisocyanate produces phenylcarbamic acid, which releases carbon dioxide to produce aniline. Addition to phenylisocyanate yields 1,2-diphenylurea. It should remarked that under conventional heating in comparable conditions did not produce the complete conversion of the starting material and gave low yields of the desired monoureas (Table 1, entries 2 and 7).
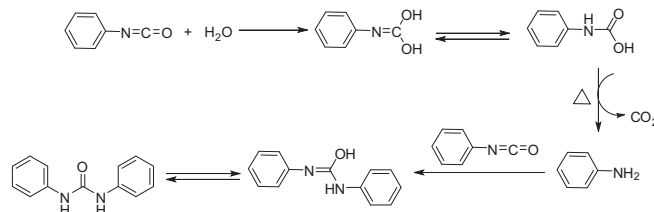
Scheme 1. Reactions leading to the formation of phenylurea in the presence of water.

Triazinyl urea **3a** was characterized by NMR techniques. The NH moieties of the urea group were differentiated by 1D-NOESY experiments, finding that Ph–NH-3 is deshielded with regard to triazine-NH-1. This deshielding must be a consequence of the formation of an intramolecular hydrogen bond with a nitrogen atom of the triazine ring (Fig. 1a). The NH_2 group shows two signals at $\delta=7.74$ and 7.85. This effect has been shown in related triazinediamines and is due to a restricted rotation of the aminotriazine bond.[28] Variable temperature experiments did not produce the coalescence of the NH groups. In consequence thermodynamic parameters of the rotation process were determined by 2D-EXSY experiments at 298 K, temperature of a slow process, in DMSO.
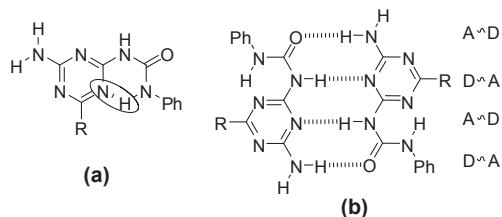
Fig. 1. (a) Intramolecular hydrogen bond of the triazine ring. (b) Dimers stabilized by quadruple hydrogen bonds.

Rate constants can be deduced from the spectra according to the following equation:

$$R = -\ln A/\tau_m = -X(\ln \Lambda)X^{-1}/\tau_m$$

where $A_{ij}=I_{ij}/M_j$, τ_m is the mixing time. $I_{ij}(\tau_m)/M_j$ and X are the square matrix of eigenvectors of A_i such that $X^{-1}AX=\Lambda=\text{diag}(\lambda_i)$, with λ_i the ith eigenvalue of A. I_{ij} can be deduced by measuring the volume of each peak intensity directly from the spectrum. M_j is the volume of the diagonal peak of the spectrum registered with a mixing time close to 0 and without any chemical exchange.