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Multicomponent Reactions

1,3,5-Triazinanes as Formaldimine Surrogates in the Ugi Reaction

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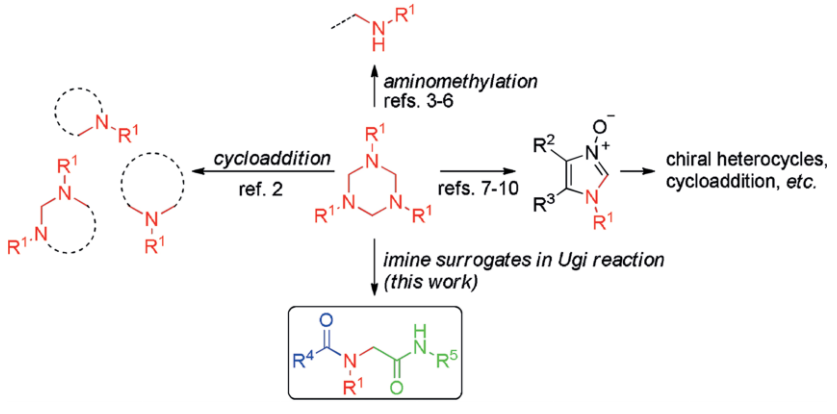
Abstract: In the present study, a new synthetic strategy towards *N*-acylated glycinamides was developed by the use of 1,3,5-triazinanes as formaldimine surrogates in the Ugi reaction. The targeted products were obtained in a combinatorial, diversity-oriented fashion in good yields. Further modifications allowed us to adapt this procedure for the one-pot two-step syntheses of a local anesthetic druglidocaine and several unsymmetrically substituted diketopiperazines.

1,3,5-Trisubstituted hexahydro-1,3,5-triazines, also referred to as 1,3,5-triazinanes or triazacyclohexanes, were introduced by Reinfield in 1902[1] and are commonly used in organic synthesis as stable, easily accessible formaldimine surrogates. For example, 1,3,5-triazinanes readily participate in the Lewis acid-promoted cycloaddition reactions. Numerous variants of the latter published over the last 3 years include [*n*+2] (triazinane as an imine surrogate), [*n*+4] or [*n*+2+2] (triazinane as a formal 1,4-dipole) and [*n*+3] (triazinane as a formal 1,3-dipole) cycloadditions.[2] In these reactions triazinanes were utilized as donors of *C-N*, *C-N-C*, *N-C-N* or *C-N-C-N* fragments for the construction of 5-, 6-, 7- and 8-membered nitrogen heterocycles. In 2015, Krische and co-workers published a ruthenium-catalyzed hydroaminomethylation of allenes and 1,3-dienes with 1,3,5-triazinanes.[3] Later on, asymmetric Mannich-type reactions with 1,3,5-triazinanes were published[4] as well as iridium-catalyzed aminomethylation of conjugated enynes[5] and rhodium-catalyzed C3-aminomethylation of indoles.[6] Another common transformation is the condensation of 1,3,5-triazinanes with α-hydroxyimino ketones to form 1,4,5-trisubstituted imidazole *N*-oxides. This reaction was a key step in the construction of potent mitogen-activated protein kinase p38 inhibitors.[7] Moreover, these imidazole *N*-oxides were further modified to obtain chiral nitrogen heterocycles[8] and chiral ionic liquids[9] or used as 1,3-dipoles in cycloaddition reactions.[10] 1,3,5-Triazinanes also served as a scaffold for peptide macrocycles – inhibitors of coagulation factor XII with K_i values in the low nanomolar range.[11] Unusual rhodium-catalyzed annulation of *N*-sulfonyl-1,2,3-triazoles with 1,3,5-triazinanes was reported recently by Bao.[12] In this reaction triazinane acts as a formal donor of both *C-N-C* and *N-C-N* fragments, and the final products are octahydro-1*H*-purine derivatives (Scheme 1).



Scheme 1. Known synthetic transformations of 1,3,5-triazinanes and the reaction investigated in this work.

Despite being a well-studied class of synthetic building blocks and their resemblance of formaldimines, 1,3,5-triazinanes remain scarcely explored in multicomponent reactions typical for imines. One rare example is the synthesis of 3-unsub-

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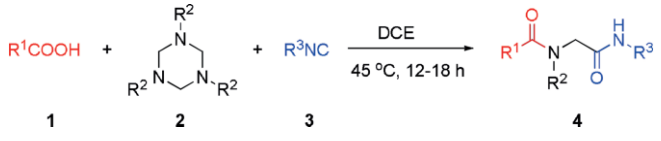
stituted tetrahydroisoquinolinic acids via the Castagnoli–Cushman reaction of triazinanes with homophthalic anhydride.[13] Surprisingly, however, there are no examples of the Ugi reaction involving 1,3,5-triazinanes as formaldimine surrogates in the literature. Puzzled by this fact, we set off to fill this gap and report the results of our findings herein.

Initially, 1,3,5-triphenyltriazinane, benzoic acid and *tert*-butyl isocyanide were chosen as model substrates for the optimization of the reaction conditions. Luckily, compound **4m** was isolated in nearly quantitative yield after stirring a solution of a stoichiometric mixture of the three starting materials in dichloroethane for 12 h at 45 °C. Hence, no further optimization was attempted, and these conditions were applied to all further experiments. The reaction with isonicotinic acid (compound **4c**) was the only exception and was carried out in methanol due to poor solubility of the acid in dichloroethane.

Next, a series of experiments were carried out with 16 triazinanes, 14 isocyanides and 21 acids to explore the reaction scope (Scheme 2, Figure 1). In most cases, glycine derivative **4** was the only detectable reaction product, isolated in moderate to nearly quantitative yields. However, when pivalic acid was used, iminoimidazoline **5** was isolated along with the targeted product **4o**. Apparently, steric bulk around the carboxylic acid anion impedes its addition to the intermediate nitrilium ion, slowing down the formation of an Ugi adduct. At the same time, a competing reaction occurs either as an acid-promoted [2+2+2] cycloaddition or as a stepwise addition of a second formaldimine molecule to the nitrilium ion followed by ring closure (Figure 2).



Scheme 2. Synthesis of glycinamides **4**. Reactions carried out with **1** (0.6 mmol), **2** (0.2 mmol) and **3** (0.6 mmol).

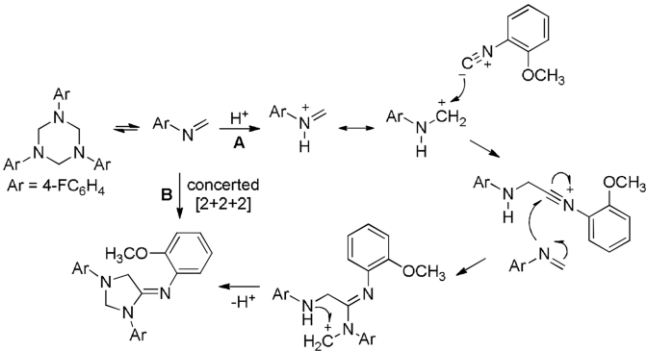


Figure 2. Proposed mechanism of formation of compound **5**.

Notably, with a proper choice of reagents, the presented methodology can be applied for the synthesis of both small glycine derivatives (such as **4b** and **4g**) and short peptoids (**4e**).

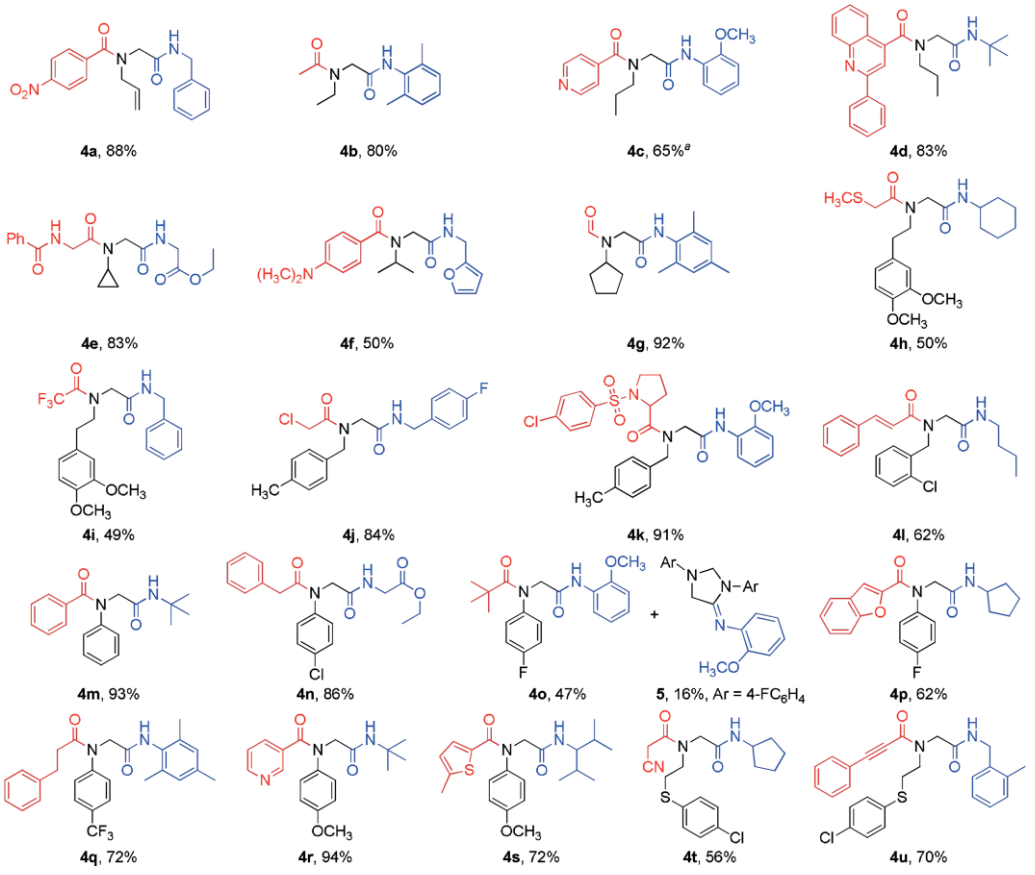
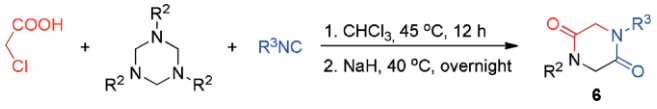


Figure 1. Glycinamides synthesized in this work. [a]Reaction carried out in MeOH for 36 h.

As chloroacetic acid can be employed in the reaction, an intramolecular S_N2-type ring closure can be envisioned in analogy to our previous report,[14] which would open a straightforward entry to 2,5-diketopiperazines, compounds of significant importance in medicinal chemistry.[15] We applied the previously developed one-pot two-step protocol (Scheme 3) and synthesized several diketopiperazines without isolation of intermediate Ugi adducts in good overall yields (Figure 3).



Scheme 3. Synthesis of diketopiperazines **6**.

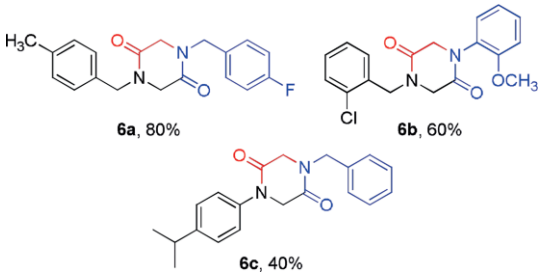
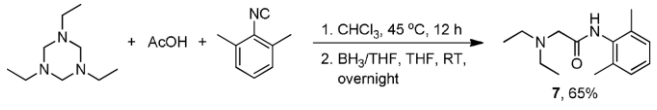


Figure 3. Diketopiperazines **6a**–**c** synthesized in this work.

Finally, we noticed that one of the synthesized compounds (glycinamide **4b**) resembles a well-known local anesthetic drug lidocaine. Earlier it was shown that a tertiary amide group in Ugi adducts can be selectively and efficiently reduced with BH_3•SMe_2 or BH_3•THF.[16] To our delight, BH_3•THF proved to be efficient in present case as well, and we were able to obtain lidocaine in a one-pot fashion without isolation of **4b** in 65 % overall yield (Scheme 4).



Scheme 4. Synthesis of lidocaine.

In conclusion, we have demonstrated that 1,3,5-triazinanes can be successfully used as formaldimine surrogates in the Ugi reaction to construct N^2-acylated glycinamide derivatives and short peptoids. Moreover, post-MCR modifications allowed us to adapt the proposed method for one-pot synthesis of diketopiperazines and lidocaine. The practical simplicity and the availability of reagents to construct complex products in a controlled diversity fashion make this method particularly useful for drug discovery.

Experimental Section

General Information: NMR spectroscopic data were recorded with Bruker Avance 400 spectrometer (400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C) in [D_6]DMSO or $CDCl_3$ and were referenced to residual solvent proton signals (δH = 2.50 and 7.26 ppm, respectively) and solvent carbon signals (δ_C = 39.52 and 77.00 ppm, respectively). The AA′XX′ and AA′XX′Y proton systems of *para*-disubstituted and monosubstituted phenyl rings, respectively, are not seen clearly in the ^{1}H NMR spectra and therefore the "apparent" coupling constants for observed "doublets" and "triplets" of the corresponding aromatic protons are given. DEPT spectra were used for assignment of carbon atoms signals. Melting points were determined with a Stuart SMP30 instrument and are uncorrected. Mass spectra were recorded with a Bruker Maxis HRMS-ESI-qTOF spectrometer (electrospray ionization mode).

General Procedure A. Synthesis of Glycinamides 4: A solution of isocyanide (0.6 mmol) in 0.3 mL of dichloroethane and a solution of carboxylic acid (0.6 mmol) in 0.3 mL of DCE were added sequentially to a stirred solution (suspension) of triazinane (0.2 mmol) in 0.3 mL of DCE in a screw-cap vial. The reaction mixture was stirred at 45 °C for 12–18 h (TLC monitored). After full consumption of the starting material the solvent was evaporated and the residue was separated by column chromatography on silica eluted with 3 % to 20 % acetone in CH_2Cl_2.

Due to poor solubility of isonicotinic acid synthesis of compound **4c** was carried out in methanol following General procedure A.

General Procedure B. Synthesis of Diketopiperazines 6: Crude glycinamides were prepared following the general procedure A. The residue after evaporation of $CHCl_3$ was dissolved in anhydrous THF, then NaH (60 % in oil, 26 mg, 0.66 mmol) was added in portions and the resulting suspension was stirred at 40 °C overnight. The reaction was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. Organic extracts were dried with $MgSO_4$, then filtered and the solvent was distilled off. Diketopiperazines were isolated by column chromatography using acetone/dichloromethane as eluent.

Acknowledgments

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Keywords: Molecular diversity · Multicomponent reactions · Synthetic methods · 1,3,5-Triazinanes · Ugi reaction

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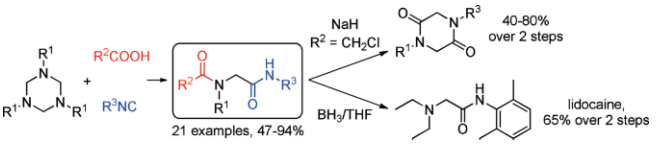

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