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Squaric acid is a suitable building-block in 4C-Ugi reaction: access to original bivalent compounds

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ABSTRACT

The 4C-Ugi reaction requires an acidic component as one of the building-blocks. We report here the first use of squaric acid for this reaction to access original symmetrical compounds. The scope and conditions of the reaction were explored.

During the past decade, isocyanide based multicomponent reactions (IMCR) gained significant interest within the scientific community as an efficient, convenient, time-saving, and atom-economical approach to rapidly generate chemical diversity. IMCRs are easily performed using readily available starting materials and tolerate a variety range of functional groups. Variations and subsequent transformations provide access to a fairly large number of unique structures that would otherwise require lengthy preparations.[1,2]

The Ugi reaction usually refers to the reaction between an amine (usually a primary amine; less often ammonia, or a secondary amine), a carbonyl compound (aldehyde or ketone), an isocyanide, and a carboxylic acid.[3] Carboxylic surrogates like carbonic[4] or thiocarbonic acids, thiocarboxylic acids,[5] hydrazoic acid,[6] isocyanic[7] and isothiocyanic acids, phenol,[8] and thiophenol were also successfully used in Ugi-type reaction.[9] Squaric acid is a diacid that exhibits two acidic hydroxyl groups with pK_a values of 0.54 and 3.48, respectively, as well as two highly polarized carbonyl groups.[10] This structure provides not only unique versatile proton acceptor carbonyl groups[11] but also binding sites to metal ions.[12] Since the work of Cohen[13] in 1959, many examples of the use of squaric template (Fig. 1) have been described particularly in the fields of bioorganic and medicinal chemistry.[14] Medicinal chemists use squaric template as either a linker, or a precursor of acidic or metal binding functions.[15] We have ourselves developed rapid parallel synthesis procedures to access bioactive squaramides, inhibitors of aggrecanase.[16] Other teams have disclosed squaramides with various biological activities such as kinase inhibition,[17] $CXCR_2$ or vitronectin receptor modulation,[18] potassium channel blockade.[19]

Interestingly, squaric acid could also be useful for the synthesis of dimeric bioactive compounds. The design of symmetrical bivalent ligands[20] has already been successfully applied to various pharmacological targets such as GPCRs, channels, and transporters.[21]

Herein we report the first use of squaric acid as the acid component in the 4C-Ugi reaction. This allows the rapid access to a variety of original symmetrical squaramides in moderate to good yields.

The reaction is a double 4C-Ugi reaction that uses the two acidic functions of squaric acid to give squaramides of general formula A (Fig. 2) as a mixture of four diastereoisomers. A proposed mechanism of this reaction, which may be considered as a Ugi-Smiles extension,[22] is presented in Scheme 1.

The 4C-Ugi reaction with squaric acid was examined with benzylisocyanide, *p*-toluidine, and *p*-chlorobenzaldehyde (Table 1) to optimize reaction conditions. Methanol and isopropanol, that are classical for Ugi reaction, were selected as solvents. We varied both concentrations and temperature. Amine, aldehyde, isocyanide, and squaric acid were used in 1:1:1:0.5 proportions. A one-pot sequential procedure was used. First, pre-formation of the imine was performed by mixing the aniline and the aldehyde for 45 min. Then squaric acid was added to form the iminium intermediate. After 10 min, isocyanide was finally added. The mixture was reacted overnight. The product was obtained by a simple work-up as it precipitates. Under these reaction conditions, the synthesized dimer **1** is a mixture of the meso isomer **1a** and the racemate **1b** (Table 1). The existence of conformers

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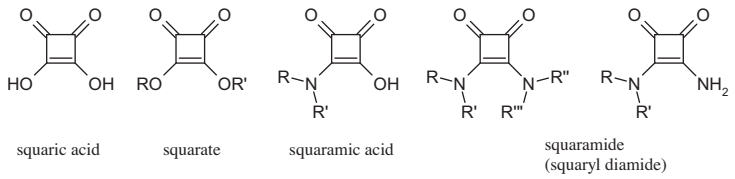


Figure 1. Squaric-based templates.

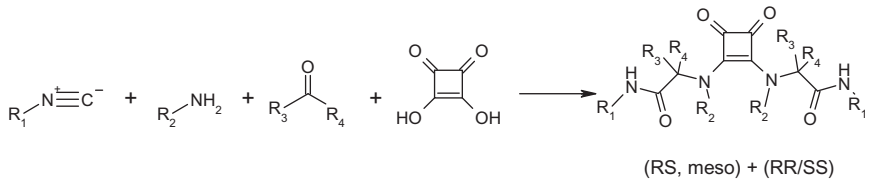
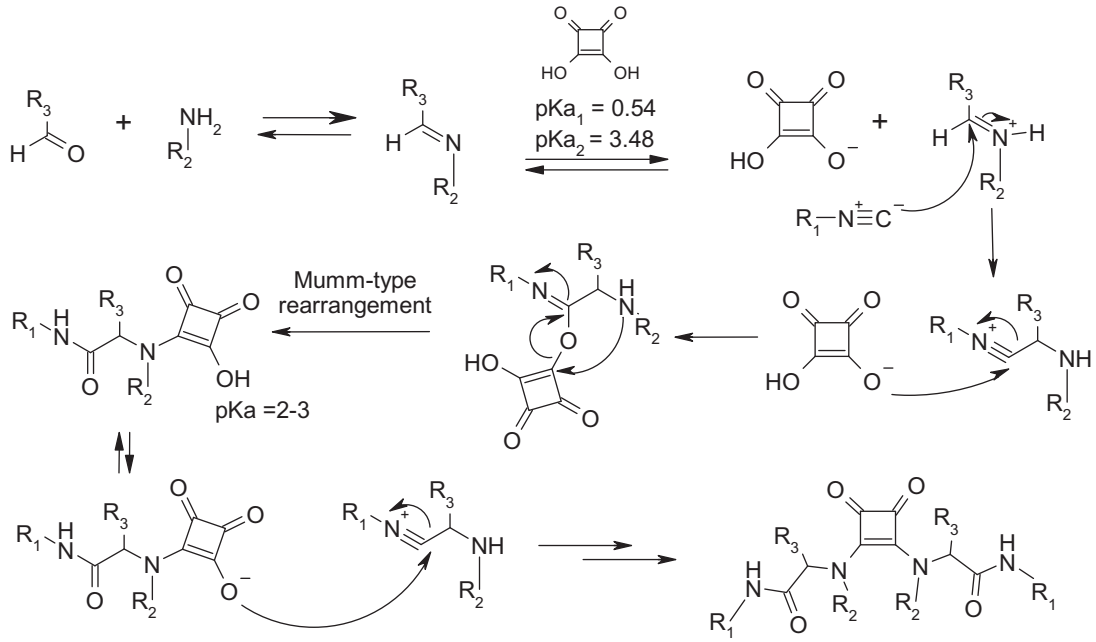


Figure 2. Double 4C-Ugi.



Scheme 1. Proposed mechanism of the double 4C-Ugi reaction using squaric acid.

was evidenced by LC–MS-TOF-MS and NMR. In solution we observed the splitting and broadening of several resonances in the ^{1}H NMR spectra at room temperature. It has already been reported that the restricted rotation around the C–N bonds of squaramides lead to a mixture of anti/syn conformers.[23,24]

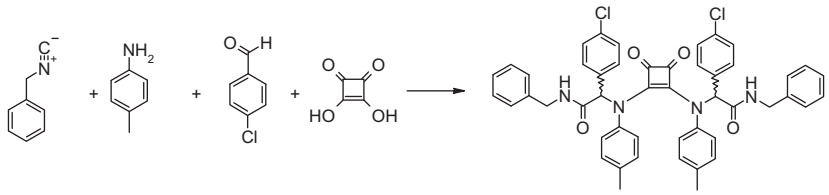
The best yield was obtained using methanol as the solvent, at room temperature, with a squaric acid concentration of 0.1 M (concentration corresponding to the measured solubility of squaric acid in methanol). When the reaction was carried out in more concentrated (0.5 M) or more diluted (0.05 M) medium, yield decreased. Same results were obtained at higher temperature (50 °C) or when using isopropanol as the solvent. We next applied our best conditions (Table 1, entry 1) to explore the scope of the reaction (Table 2).

The reaction tolerated aromatic, benzyl-, and aliphatic isocyanides providing the desired products in moderate to good yields (**2**–**5**, 55–73%). Influence of the amine component was assessed using aliphatic and aromatic amines (**2**, **11**–**15**, 25–73%). Aliphatic amines like butylamine and cyclopropanemethylamine provided the desired compounds in lower yields of 25% (**14**) and 42% (**15**), respectively. In this reaction, the formation of the iminium intermediate is critical.[26] Less basic amines like anilines gave the expected compounds in better yields than more basic aliphatic amines (Table 2). Already observed with carboxylic acids, this behavior is even more pronounced with the more acidic squaric acid (pK_a values of 0.54 and 3.48, significantly lower than the average carboxylic acid). The high acidity of squaric acid is favorable for the reaction with anilines and aromatic aldehydes for which the very low basicity of the Schiff base formed is highly detrimental for the obtention of the iminium ion.

The lower yields obtained with aliphatic amines could be due to incomplete formation of the imine. Indeed, the equilibrium amine/imine could be displaced in favor of the amine by protonation of the latter by squaric acid. Such equilibrium displacement may not be encountered for anilines since (1) the corresponding imines are conjugated and (2) anilines are less basic.[27,28]

For the carbonyl component, the scope is as expected for a 'classical' 4C-Ugi reaction. Aliphatic or aromatic aldehydes give the desired compounds in good yields (Table 2). Aliphatic ketones are slightly less reactive and arylketone, described as the least reactive carbonyl component for 4C-Ugi reaction, did not yield compound **7**.

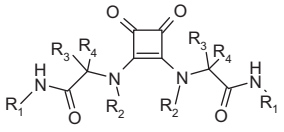
Table 1
Optimization of the synthesis of **1a** and **1b**



Entry	Solvent[a]	*T* (°C)	[squaric acid] (M)	Yield[b] (%)
1	MeOH	20	0.1	69
2	MeOH	20	0.05	42
3	MeOH	20	0.5	44
4	MeOH	50	0.1	33
5	*i*PrOH	20	0.1	21
6	*i*PrOH	50	0.1	40

[a] Measured solubility of squaric acid in MeOH: 0.09 M or in *i*PrOH: 0.02 M.
[b] Yield of the mixture of diastereoisomers.

Table 2
Synthesis of symmetrical squaramides **1**–**15** via 4C-Ugi reaction



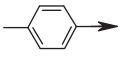
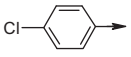
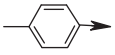
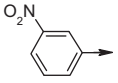
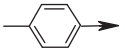
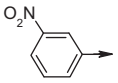
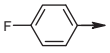
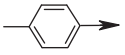
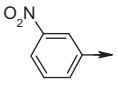
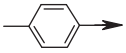
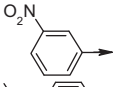
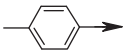
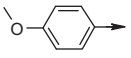
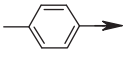
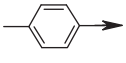
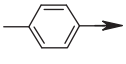
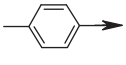
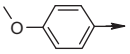
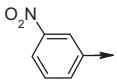
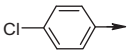
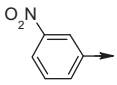
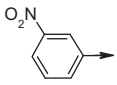
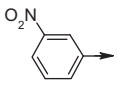
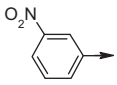
Compd	R_1-	R_2-	R_3-	R_4-	Yield[a]
1				H-	69
2				H-	73
3				H-	55
4				H-	68
5				H-	58
6				H-	45
7				Me-	0
8				H-	60[b]
9					40[25]
10			H-	H-	32

Table 2 (*continued*)

Compd	R_1-	R_2-	R_3-	R_4-	Yield[a]
11				H-	54
12				H-	64
13				H-	55
14				H-	25
15				H-	42

[a] Yield of diastereoisomer mixture.
[b] Purified by flash chromatography.

In conclusion, we report the first use of squaric acid as a component of the 4C-Ugi reaction. We describe a new, simple, and efficient application to the one-pot direct access to original squaric-based symmetrical compounds using mild reaction conditions and a straightforward purification process. The access to squaramic acids via a 'mono-4C-Ugi' reaction is currently under investigation in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.11.077.

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24. In our case, raising the temperature (up to 80 °C) in the NMR experiments did not allow coalescence of the signals.
25. *Typical procedure for the preparation of symmetrical squaramides (**9** as example)*: *p*-toluidine (2 equiv) is added to cyclohexanone (2 equiv) in (1.5 mL) MeOH. After stirring 45 min at room temperature, squaric acid (0.25 mmol, 1 equiv) in solution in MeOH (1 mL) is added and the mixture is stirred 5 min. Benzyl isocyanide (2 equiv) is finally added and the reaction is stirred overnight at room temperature. The precipitate is filtrated and washed with diethyl ether to give the desired compound **9** as a white solid (72 mg, 40%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.62 (br s, 2H, N*H*), 7.22–7.32 (m, 10H, *H*ar), 7.00–7.08 (m, 8H, *H*ar), 4.24 (d, J = 5.4 Hz, 4H, 2CH_2), 2.29 (br m, 10H, 2 CH_3 + 2CH_2), 1.85 (br m, 4H, 2CH_2), 1.28–1.39 (m, 12H, 6CH_2). tr_{LC-MS} = 3.70 min. ^{13}C NMR (75 MHz, DMSO-d_6) δ 180.9, 171.1, 139.7, 137.8, 136.6, 129.1, 128.6, 127.7, 127.2, 69.9, 43.4, 34.3, 24.4, 22.8, 21.2. Purity 97%. MS (ESI$^+$) m/z = 723 $[M+H]^+$. HRMS: calcd for $C_{46}H_{50}N_4O_4$, (MH^+) 723.3910, found 723.3915.
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27. In order to verify our hypothesis, we try to obtain compound **14** by pre-forming the imine in the presence of a dehydrating agent in order to avoid the imine hydrolysis when adding squaric acid. Unfortunately, the yield could not be improved by this way.
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