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Synthesis of [1,2,4,5]tetrazino[6′,1′:2,3]imidazo[4,5-*c*]isoquinolin-5-ones by microwave-assisted three-component reaction

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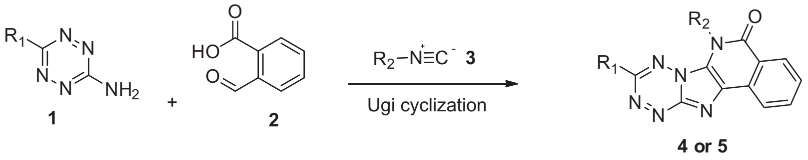
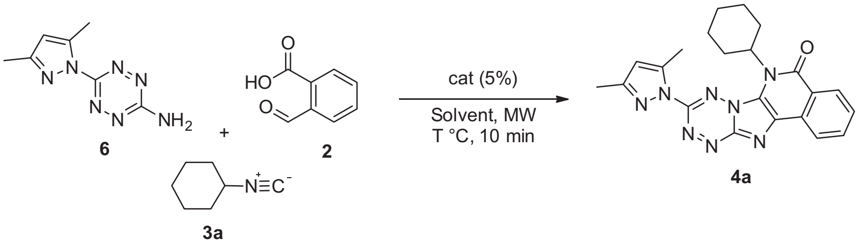
ABSTRACT

An efficient and original Ugi multicomponent reaction of aminopyridines and aminopyrimidines is reported. Starting from aminotetrazine **6** or **7**, an isocyanide and an *ortho*-carboxybenzaldehyde, tetrazinoimidazoisoquinolinones were isolated, after few minutes of microwave irradiation, in good to excellent yields. The scope of this method was extended by using different isocyanides.

In the last decades, multicomponent reactions (MCR) have emerged as a powerful tool for the synthesis of complex scaffolds.[1] Isocyanide based MCRs are frequently exploited because of the special reactivity of this functional group. Among them, the most famous reactions are the Passerini,[2] Ugi,[2a,3] and recently the Groebke–Blackburn 3-component reactions,[4] which affords imidazo[1,2,*a*] annulated heterobicyclic compounds. This type of structure is found in compounds showing a wide range of biologi-



Scheme 1. Multicomponent synthesis.



Scheme 2. Preparation of **4a**.

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Table 1
Optimization of the conditions for the formation of **4a**

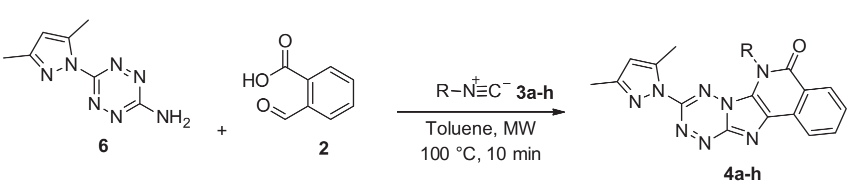
Entry	Solvent	Heat	Catalyst	Yield[a]
1	MeOH	MW, 120 °C, 10 min	–	25%
2	EtOH	MW, 120 °C, 10 min	–	38%
3	*i*-PrOH	MW, 120 °C, 10 min	–	62%
4	H_2O	MW, 100 °C, 10 min	–	70%
5	Toluene	MW, 100 °C, 10 min	–	76%
6	Toluene	RT	–	Traces
7	Toluene	110 °C	–	10%
8	Toluene	MW, 100 °C, 10 min	NH_4Cl	60%
9	Toluene	MW, 100 °C, 10 min	$Sc(OTf)_3$	Traces
10	Toluene	MW, 100 °C, 10 min	TsOH	Traces

[a] Yields are given for isolated product; MW: microwave irradiations; RT room temperature.

cal activities such as antiulcer,[5] hypnotic,[6] anxiolytic,[7] and many other biological activities.[8] Indeed, new isocyanide based MCRs are frequently published, allowing several degrees of structural diversity.[9]

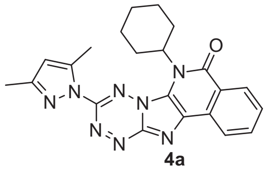
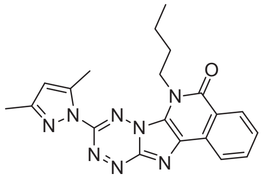
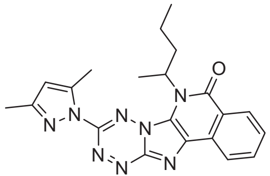
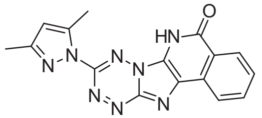
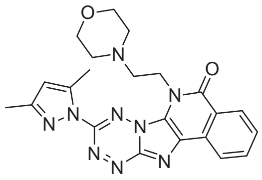
The well-known Ugi four-component condensation between aldehydes, isocyanides, amines and carboxylic acids generally affords N-substituted α-acylamino carboxamides.[10] Lactams were also obtained by using bifunctional reagents.[11] Recently following this strategy, Beifuss synthesized new pyrido[2′,1′:2,3]imidazo[4,5-*c*]isoquinolin-(6*H*)-one skeletons by a microwave-assisted three-component reaction using 2-aminopyridine, 2-carboxybenzaldehyde and an isocyanide.[11a]

Based on the interests of our group in the synthesis of functionalized imidazo[1,2-*b*][1,2,4,5]tetrazines,[12] we disclose herein a



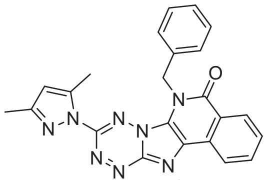
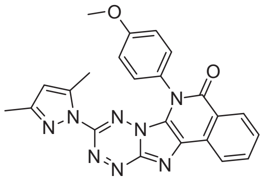
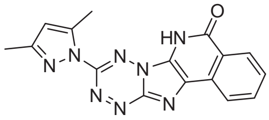
Scheme 3. Variation of the isocyanide.

Table 2
Synthesis of compounds **4a**–**g**

Entry	Isocyanides	Products	Yields[a]
1	*c*-Hexyl isocyanide **3a**	 **4a**	76%
2	*n*-Butyl isocyanide **3b**	 **4b**	81%
3	2-Pentyl isocyanide **3c**	 **4c**	Traces
4	*t*-Butyl isocyanide **3d**	 **4d**	61%
5	2-Morpholinoethyl isocyanide **3e**	 **4e**	68%

(*continued on next page*)

Table 2 (*continued*)

Entry	Isocyanides	Products	Yields[a]
6	Benzyl isocyanide **3f**	 **4f**	71%
7	*p*-Methoxyphenyl isocyanide **3g**	 **4g**	62%
8	Trimethylsilyl cyanide **3h**	 **4d**	71%

[a] Yields are given for isolated product.

new use of substituted amino[1,2,4,5]tetrazines **1** in the modified Ugi multicomponent reaction (Scheme 1).

First, we started using an equimolar amount of aminotetrazine **6**, 2-carboxybenzaldehyde **2** and cyclohexyl isocyanide **3** in methanol (Scheme 2). The resulting mixture was irradiated at 120 °C for 10 min, which afforded the desired functionalized imidazo[1,2-*b*][1,2,4,5]tetrazine in 25% yield (Table 1, entry 1). The replacement of methanol by ethanol (Table 1, entry 2) and then by *iso*-propanol (Table 1, entry 3) allowed us to improve the yield, affording the imidazotetrazine **4a** in 38% and 62% yield, respectively.

Compound **4a** was finally isolated in 70% yield using water as solvent, and in 76% yield with toluene (Table 1, entries 4 and 5). As the best result was obtained with toluene, which is known for its poor microwave absorbability, we thought that thermal conditions should be tested. However, these conditions were less efficient (Table 1, entries 6 and 7); that is, at room temperature, the starting material was recovered and in refluxing toluene, the desired product **4a** was isolated in low yield. Consequently, microwave irradiations and toluene as solvent were thus chosen for the rest of the study. Then, the use of different additives was then investigated. A dramatic decrease in yield was observed either with ammonium chloride (Table 1, entry 8),[13] or surprisingly, scandium triflate.[4] Moreover, *p*-toluene sulfonic acid[14] totally inhibited the reaction (Table 1, entries 9 and 10).

The variation of the isocyanide partner **3** was then studied (Scheme 3, Table 2).

Alkyl isocyanides generally gave good results (Table 2), except in the case of 2-pentyl isocyanide (Table 2, entry 3), which only led to traces of expected product and mostly to the starting materials. Surprisingly, in the case of *tert*-butyl isocyanide, only compound **4d** was isolated in 61%, proving the relative lability of the *tert*-butyl group without acidic treatment (Table 2, entry 4).[14] Noteworthy, **4d** can also be synthesized using trimethylsilyl cyanide as starting material (Table 2, entry 8).[15] More functionalized isocyanides can also be employed, as 2-morpholinoethyl isocyanide affords compound **4e** in 68% yield (Table 2, entry 5). Finally, benzyl and 4-methoxyphenyl isocyanides proved to be good partners for the reaction, as compounds **4f** and **4g** were obtained in 71% and 62% yield, respectively (Table 2, entries 6 and 7).

Table 3
Synthesis of compounds **5a**–**g**

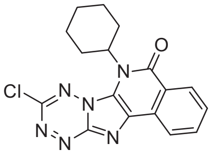
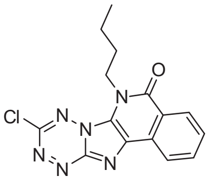
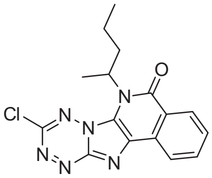
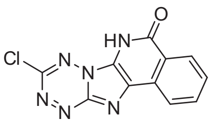
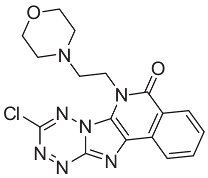
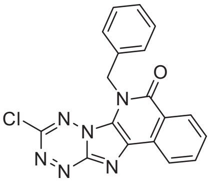
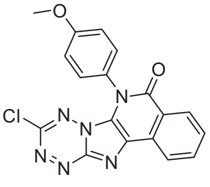
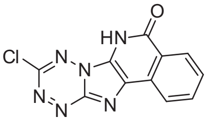
Entry	Isocyanides	Products	Yields[a]
1	*c*-Hexyl isocyanide **3a**	 **5a**	61%
2	*n*-Butyl isocyanide **3b**	 **5b**	79%
3	2-Pentyl isocyanide **3c**	 **5c**	53%
4	*t*-Butyl isocyanide **3d**	 **5d**	57%
5	2-Morpholinoethyl isocyanide **3e**	 **5e**	Traces

Table 3 (*continued*)

Entry	Isocyanides	Products	Yields[a]
6	Benzyl isocyanide 3f	 **5f**	66%
7	*p*-Methoxyphenyl isocyanide **3g**	 **5g**	Traces
8	Trimethylsilyl cyanide **3h**	 **5d**	Traces

[a] Yields are given for isolated product.

Next, we tried to introduce a chlorine atom on the scaffold, which could allow coupling reactions at a later stage. Hence, 6-chloro-1,2,4,5-tetrazin-3-amine **7** was employed as starting material.[16] The same behavior as pyrazolo derivative **6** was generally observed with the different isocyanides (Table 3, Scheme 4). However, this amine did not lead to degradation with 2-pentyl isocyanide and compound **5c** was isolated in 53% yield (Table 3, entry 3). Decomposition was nevertheless noticed with 2-morpholinoethyl, *p*-methoxyphenyl isocyanides and trimethylsilyl cyanide (Table 3, entries 5, 7, and 8), as only traces of the desired compounds were obtained.[18]

The structure of **5a** was confirmed using X-ray diffraction. (Fig. 1).[17] Two independent molecules were found in the cell unit. They only differ from the torsion angle between the cyclohexyl ring and the hetero-polycyclic moiety, that is, molecule I: C(12)–N(11)–C(20)–C(21) = −52.6(4)°, molecule II: C(62)–N(61)–C(70)–C(71) = −52.6(4)°. The polycyclic skeleton adopts an almost planar conformation, with, for example, dihedral angles C(12)–N(11)–C(8)–N(6) = −171.8(3)°, C(14)–C(9)–N(10)–C(5) = −177.5(3)°. The bond lengths C(8)–N(11), C(8)–C(9) and C(8)–N(6) and the dihedral angle N(6)–C(8)–N(11)–C(20) = 13.4(5)°, illustrate the sp^2 character of C(8) and N(11), respectively.

In this Letter, we have shown that the modified Ugi multicomponent reaction can be generalized to the use of amino[1,2,4,5]tetrazines. The desired [1,2,4,5]tetrazino [6′,1′:2,3]imidazo[4,5-*c*]isoquinolin-5-ones were generally isolated in good to excellent yield. Studies on the functionalization of the 3-chloro-imidazo[1,2-*b*][1,2,4,5]tetrazine derivatives are currently in progress and results will be published in due course.

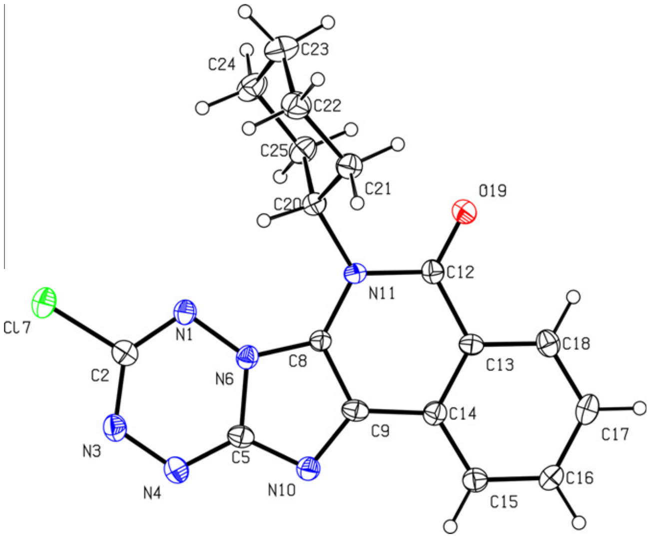


Figure 1. ORTEP diagram derived from the single-crystal X-ray analysis of compound **5a**.

Acknowledgment

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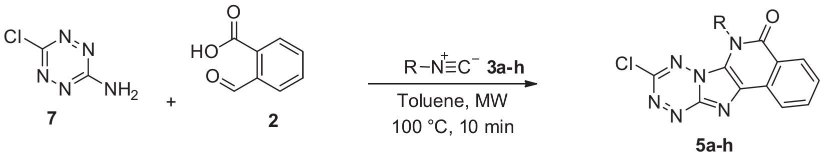

Scheme 4. Preparation of compounds **5**.

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17. Crystallographic study: The structure of compound **12** has been established by X-ray crystallography (Fig. 1). Single red crystals of **12** were obtained by slow evaporation from methanol/dichloromethane (20/80) mixture. All reflections were used for unit cell refinement: $a = 6.8958$ (2) Å, $b = 14.1435$ (7) Å, $c = 17.1546$ (1) Å, $\alpha = 76.823$ (5)°, $\beta = 80.221$ (4)°, $\gamma = 89.914$ (6)°. Space group: $P\overline{1}$, $Z = 2$, $d = 1.469\ \mathrm{g\ cm^{-3}}$, μ (Cu, $K\alpha$) = $2.274\ \mathrm{mm^{-1}}$. 5688 Unique reflections were measured with final $R = 6.57\%$ ($I > 2\sigma(I)$). All the data were collected with a *R*-axis Rapid Rigaku MSC diffractometer using the CuKα radiation and a graphite monochromator. The structure was solved by direct methods Shelx 86 and refined using Shelx 97 suite of programs.[a,b] The program PLATON[c] was used for analysis and drawing figures. The positions of the H atoms were deduced from coordinates of the non-H atoms and confirmed by Fourier synthesis. The non-H atoms were refined with anisotropic temperature parameters. H atoms were included for structure factor calculations but not refined. CCDC 805069 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.uk/conts/retrieving.html (or from Cambridge Crystallographic Data Centre, University Chemical Lab, 12 Union Road, Cambridge, CB2 1EZ, U.K.; e-mail: deposit@ccdc.cam.ac.uk.) (a) Sheldrick, G. M.; Kröger, C.; Goddard, R. *SHELX 86 in Crystallographic Computing 3*; Oxford University Press: New York, 1985. pp 175–189; (b) Sheldrick, G. M. *SHELX 97, Program for the Refinement of the Crystal Structures*; University of Göttingen: Germany, 1997; (c) Spek, A. L. *Acta Crystallogr., Sect. A* **1990**, *46*, 34.
18. *General procedure*: A 2–5 mL microwave vial was charged with the appropriate aminotetrazine (1.0 equiv), 2-carboxybenzaldehyde (1.0 equiv) and isocyanide (1.0 equiv) in toluene. The resulting solution was subjected to microwave irradiations at 100 °C for 10 min. The mixture was then filtered and the desired compound was isolated without further purification as an orange solid.