A Concise Approach Toward Tetrazolyl-Substituted Benzazocines via a Novel Isocyanide-Based Multicomponent Reaction

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Received: 20.11.2013; Accepted after revision: 04.02.2014

Abstract: The synthesis of pharmacologically relevant isoquinoline-tetrazoles and benzazocine-tetrazoles via sequential azido-Ugi and alkyne-induced ring-expansion reactions starting from cotarnine chloride are reported. A one-pot, multicomponent reaction protocol toward the ring-expanded product is also described.

Key words: alkaloids, multicomponent reaction, domino reaction, ring expansion, alkynes

Historically, the majority of new drugs have been created from natural products (secondary metabolites), or from compounds derived from natural sources. Natural products, especially alkaloids, continue to attract significant attention due to their unique ability to serve as starting points for the development of novel modulators of biomolecule function.[1] It is thought that the tendency of natural products, or natural product derived compounds to be recognized by a therapeutic protein molecule is concerned with their molecular structure, that is in itself created by a series of biosynthetic enzymes.[2] Natural products have therefore not only served as precursors for semi-synthetic derivative libraries,[3] but have also inspired significant interest in creating synthetic protocols aimed at complex, 'natural-like' novel synthetic compounds.[4]

The chemistry of cotarnine (**1**) (Figure 1) and related heterocyclic pseudo-bases has attracted considerable attention due to their diverse chemical reactivity and important biological and medicinal implications.[5]

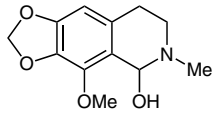

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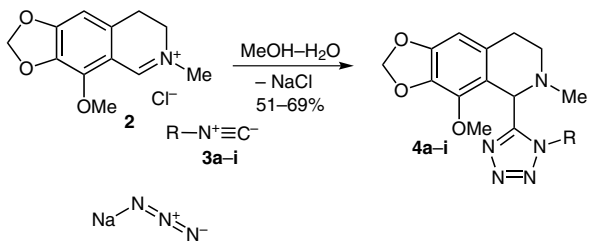
Figure 1 The structure of cotarnine (**1**)

As part of our research program on isocyanide multicomponent[6] and alkyne-induced N-heterocyclic ring-expansion reactions,[7] we became interested in studying the reactivity of cotarnine chloride (**2**) in condensation reactions with an isonitrile and sodium azide (the Ugi-azide reaction), followed by activated alkyne triggered isoquinoline ring-expansion leading to the formation of 1,5-disubstituted tetrazoles bearing isoquinoline or azocine substituents. 1,5-Disubstituted tetrazoles are important drug-like scaffolds, which are known for their ability to mimic the *cis*-amide bond conformation. Replacement of the amide bonds by surrogates in order to enhance metabolic stability and/or probe receptor specificity has become an increasingly important topic of research, as the central biological role of peptides as chemical effectors becomes more understood.[8] Apparently, the development of reliable protocols toward novel 1,5-disubstituted tetrazole derivatives has the potential to deliver small molecule probes for new or known protein receptors, thereby enabling studies on protein function.[9]

Herein, we report a concise route toward pharmacologically relevant isoquinoline-tetrazoles and previously unreported benzazocine-tetrazoles.

Originally reported in 1961, the Ugi-azide reaction involves Schiff base formation from appropriately substituted aldehydes or ketones and primary amines, followed by its reaction with an isocyanide. The resulting intermediate nitrilium ion then reacts with an azide to afford substituted tetrazoles in good yields.[10]

Initial studies concentrated on exploring the suitability of commercially available cotarnine chloride (**2**) in reactions with isonitriles **3** and sodium azide to provide the tetrazolyl-isoquinolines **4a**–**i** (Scheme 1, Table 1).



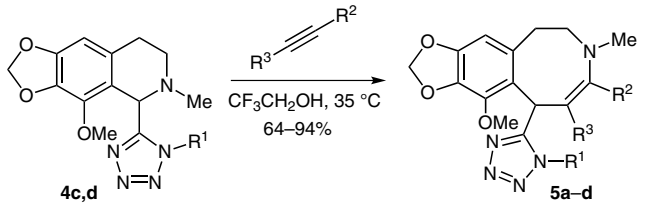
Scheme 1 Ugi-azide reaction using cotarnine chloride (**2**)

In a typical experiment, cotarnine chloride (**2**) (1 mmol), isonitrile **3** (1.2 mmol) and sodium azide (1.2 mmol) were

SYNLETT 2014, 25, 0955–0958
Advanced online publication: 11.03.2014
DOI: 10.1055/s-0033-1340861; Art ID: ST-2013-B1071-L

dissolved in a mixture of water–methanol (1:5, 5 mL), and the resulting solution stirred at room temperature for 18–24 hours (TLC monitoring). In most cases, the target tetrazolyl-isoquinolines **4** precipitated from the reaction mixtures (see the Supporting Information for details). After completion of the reaction (monitored by the disappearance of the isocyanide spot according to TLC), LC–MS analysis showed the presence of a multicomponent mixture containing compounds **4** as the major products (65–81% according to LC–MS), along with several by-products, which we were unable to isolate or identify.

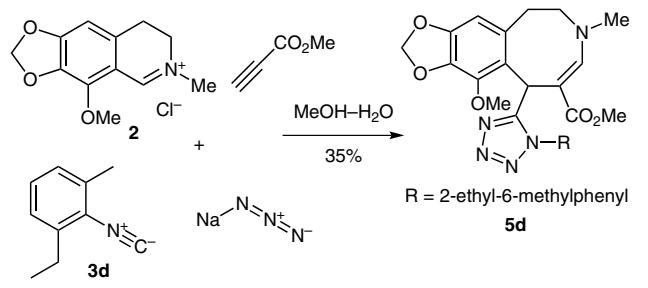
Next, the post-Ugi ring-expansion reaction was studied using isoquinolines **4c**,**d** and methyl propiolate, dimethylacetylene dicarboxylate (DMAD) or acetyl acetylene (Scheme 2).



Scheme 2 Post-Ugi ring-expansion reaction

The experimental protocol employed was analogous to that previously reported[11] for 1-arylisoquinolines. Thus, DMAD, methyl propiolate or acetyl acetylene (1.2 mmol) was added to a solution of the derivative **4c**,**d** (1 mmol) in 2,2,2-trifluoroethanol (TFE) (10 mL). The reaction mixture was stirred for four to eight hours at 35 °C (TLC monitoring). Following completion, the solvent was evaporated under reduced pressure and the residue was crystallized to give the corresponding benzazocine-tetrazoles **5a**–**d** (Scheme 2, Table 1). Being distinct from previously reported data,[11] the use of 2,2,2-trifluoroethanol instead of acetonitrile was mandatory for the efficient ring expansion in this case. We presume that the reason for this is the presence of a highly potent electron-withdrawing tetrazolyl substituent at the C1 position of the isoquinoline core, which favors the C1–N bond cleavage (S_N1-like process) after attack of the activated alkyne.

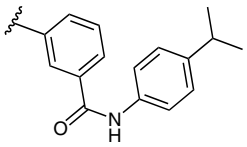
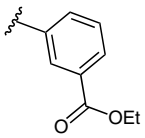
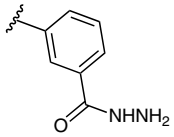
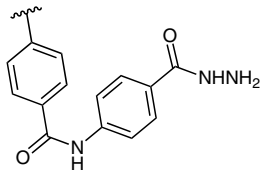
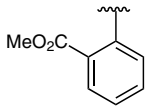
In an attempt to combine these two transformations into a single multicomponent reaction (MCR), we studied a novel four (pseudo-five) component condensation of cotarnine chloride (2), sodium azide, isocyanide 3d and methyl propiolate in methanol (Scheme 3).

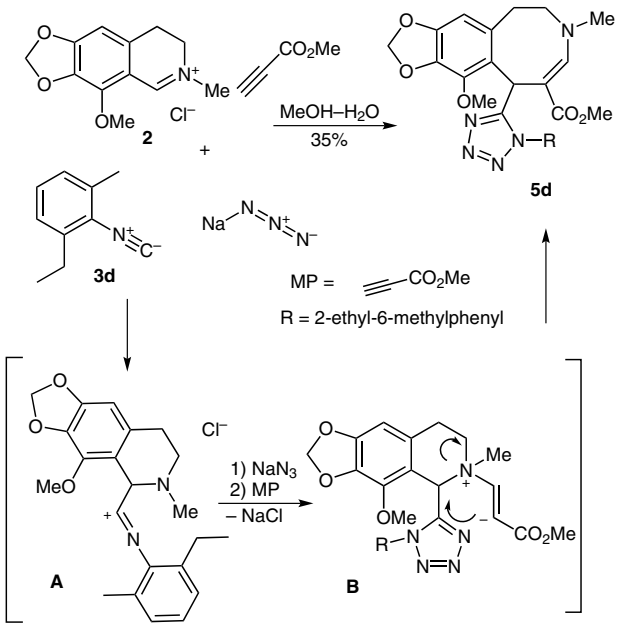


Scheme 3 MCR route towards benzazocine-tetrazoles

After stirring for 24 hours at room temperature, the solvent was evaporated and the residue was purified by flash chromatography to yield the azocine **5d** in 35% yield. A plausible mechanistic rationale for this MCR is depicted in Scheme 4. The reaction begins with the attack of the isocyanide **3d** on the C1 atom of cotarnine chloride (**2**) to yield the immonium cation **A**, which subsequently reacts with the azide anion and methyl propiolate (MP) to produce the zwitterionic intermediate **B**. Finally, intramolecular nucleophilic attack of the anion of **B** results in ring expansion to give product **5d**.

Table 1 Formation of Compounds **4a–i** and **5a–d**

Product	R	R^1	R^2	Yield (%)
4a	cyclohexyl	–	–	51
4b	cyclopentyl	–	–	53
4c	Bn	–	–	63
4d	2-ethyl-6-methylphenyl	–	–	57
4e		–	–	69
4f		–	–	58
4g		–	–	63
4h		–	–	55
4i		–	–	62
5a	Bn	H	CO_2Me	75
5b	Bn	H	CO_2Me	64
5c	Bn	COOMe	CO_2Me	94
5d	2-ethyl-6-methylphenyl	H	CO_2Me	73



Scheme 4 A plausible mechanism for the MCR

Our attempts to examine a one-pot, stepwise reaction by first combining cotarnine, the isocyanide and sodium azide, and then adding the alkyne also resulted in the formation of a multicomponent mixture, which after purification by column chromatography provided the target azocine **5d** in 38% yield.

To date, we have been unable to isolate any other low molecular weight by-products from this MCR procedure.

In conclusion, we have described the synthesis of isoquinoline-tetrazoles and benzazocine-tetrazoles via sequential azido-Ugi and alkyne-induced ring-expansion reactions.[12] A one-pot, multicomponent reaction protocol toward the ring-expanded product is also reported. Further work aimed toward optimization of the reaction conditions and a study of the scope and limitations of this procedure is underway, and the results will be reported in due course.

Acknowledgment

This work was supported by the Russian Foundation for Basic Research (grant # 13-03-00021a and grant # 14-03-93001 Viet-a).

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) **Isoquinoline-Tetrazoles 4a–i; General Procedure**
Cotarnine chloride (**2**) (1 mmol), isonitrile **3** (1.2 mmol) and NaN_3 (1.2 mmol) were dissolved in H_2O–MeOH (1:5, 5 mL), and the mixture was stirred at r.t. for 18–24 h (TLC monitoring). Products **4a**,**b** were isolated using flash chromatography (EtOAc–hexanes, from 1:50 to 1:10). Products **4c–i** precipitated from the reaction mixtures and were removed by filtration, washed with cold MeOH (15 mL) and dried in air.
5-(1-Cyclohexyl-1*H*-tetrazol-5-yl)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinoline (4a)
Yield: 189 mg (51%); colorless powder; mp 147–149 °C (EtOAc–hexanes); reaction time = 19 h. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 1.18–1.33 (m, 2 H), 1.37–1.47 (m, 1 H), 1.60–1.71 (m, 2 H), 1.72–1.79 (m, 2 H), 1.79–1.87 (m, 2 H), 1.91–1.97 (m, 1 H), 2.21 (s, 3 H), 2.56 (dt, *J* = 4.8, 11.7 Hz, 1 H), 2.64 (dt, *J* = 4.8, 16.5 Hz, 1 H), 2.79–2.86 (m, 1 H), 2.90–2.96 (m, 1 H), 3.50 (s, 3 H), 4.51–4.59 (m, 1 H), 5.18 (s, 1 H), 5.90 (d, *J* = 9.6 Hz, 2 H), 6.50 (s, 1 H). ^{13}C NMR (150 MHz, DMSO-d_6): δ = 25.1, 25.2, 25.3, 26.8, 33.1, 33.2, 42.2, 46.8, 52.7, 57.1, 59.3, 101.4, 103.3, 118.2, 129.5, 134.5, 139.9, 148.8, 154.6. HRMS (MALDI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{25}N_5O_3Na$: 394.1849; found: 394.1861.
Azocines 5; General Procedure
DMAD, methyl propiolate or acetyl acetylene (1.2 mmol) was added to a solution of derivative **4a**,**c** (1 mmol) in TFE (10 mL). The mixture was stirred for 4–8 hours at 35 °C (TLC monitoring). The solvent was evaporated under

reduced pressure and the residue was crystallized from EtOAc–hexane to give the corresponding benzazocine-tetrazole **5a–d**.

Methyl 10-(1-Benzyl-1*H*-tetrazol-5-yl)-11-methoxy-7-methyl-5,6,7,10-tetrahydro[1,3]dioxolo[4′,5′:4,5]benzo-[1,2-*d*]azocine-9-carboxylate (5a)

Yield: 350 mg (75%), pale brown solid; mp 116–118 °C; reaction time = 8 h. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.74 (dt, *J* = 5.5, 16.5 Hz, 1 H), 2.80 (s, 3 H), 2.80–2.88 (m, 1 H), 2.49 (dt, *J* = 5.5, 15.1 Hz, 1 H), 3.68 (s, 3 H), 3.78 (s, 3 H), 3.96–4.08 (m, 1 H), 5.42 (AB, *J* = 15.6 Hz, 2 H), 5.90 (s, 2 H), 6.25 (s, 1 H), 6.86 (s, 1 H), 7.00–7.44 (m, 2 H), 7.21–7.29 (m, 3 H), 7.33 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 29.9, 35.2, 45.3, 50.6, 51.6, 52.4, 60.2, 92.9, 101.3, 105.8, 121.8, 127.2 (2 C), 128.1, 128.6 (2 C), 132.9, 134.3, 136.2, 141.3, 148.1, 154.2, 159.3, 169.7. HRMS (MALDI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{25}N_5O_5Na$: 486.1747; found: 486.1758.

