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A facile and rapid route for the synthesis of novel 1,5-substituted tetrazole hydantoins and thiohydantoins via a $TMSN_3$-Ugi/RNCX cyclization

Federico Medda [a], Christopher Hulme [a,b,*]

[a] College of Pharmacy, BIO5 Oro Valley, 1580 E. Hanley Blvd, The University of Arizona, Tucson, AZ 85737, United States
[b] Department of Chemistry and Biochemistry, The University of Arizona, Tucson, AZ 85721, United States

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ABSTRACT

This Letter describes novel methodology for the rapid assembly of new and biologically appealing 1,5-substituted tetrazole-hydantoins and thiohydantoins. The product of a $TMSN_3$-Ugi multi-component reaction is treated with an excess of isocyanate or isothiocyanate to generate the final scaffold in moderate to good yields. The applicability of this solution phase methodology to the preparation of a small collection of compounds is discussed.

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In the post-genomic era, medicinal chemists have been provided with an unprecedented series of novel pharmacological targets validated with small molecules to varying degrees. Currently, many of these targets are in dire need of small molecule partners to elucidate their role in disease pathogenesis. As a result, there is an increasing need to access new dimensions in chemical space in a quest for the discovery of biologically relevant molecules in a rapid and economic fashion. To this end, studies on the discovery and utility of multi-component reactions offer an extremely attractive route to deliver a multitude of new fundamental methodologies and subsequently scaffolds for evaluation in biological systems.[1]

Specifically, the hydantoin (imidazoline-2,4-dione) scaffold represents a common motif in many biologically relevant compounds with anti-convulsant, anti-muscarinic, anti-ulcer, anti-viral, and anti-diabetic activities to name but a few.[2] Interesting examples are represented by known drugs Azimilide[3] and Fosphenytoin (Cerebyx,® Prodilantin®) and preparations of this class of molecule still attract the interest of organic and medicinal chemists as noted in recent work.[4] In analogous fashion, 1,5-disubstituted tetrazoles exist in a pharmacologically rich vein of chemical space,[5] with their value thought to reside in their capacity to act as effective *cis*-amide bioisosteres.[6] Consequently, an on-going research effort in this laboratory has been carried out to explore the utility of the so-called Ugi-azide MCR which delivers a scaffold in one step containing a 1,5-disubstituted tetrazole and either a secondary or tertiary amine, generally imparting desirable physicochemical properties on the MCR product.[7] Reported in 1961, the Ugi-azide MCR (or $TMSN_3$ modified Ugi reaction) differs from the classical Ugi MCR in that an azide **4** traps out the intermediate nitrilium ion **6** (replacing the carboxylic acid seen in the Ugi MCR) leading to the formation of the final 1,5-disubstituted tetrazole **8** (Scheme 1).[8]

In a continuation of recent studies, we herein describe a strategy based on a post-condensation modification of the $TMSN_3$-Ugi reaction product **8**, which leads to the unprecedented and pharmacologically relevant bis-heterocyclic scaffold **9** (Scheme 2). It was envisioned that the employment of ethyl glyoxalate **1** as the carbonyl component of the MCR would afford the $TMSN_3$-Ugi product **8** where subsequent treatment of **8** with an isocyanate or isothiocyanate enables rapid assembly of the target scaffold **9** in two operationally friendly synthetic operations (Scheme 2).

Thus, ethyl glyoxalate **1** and *n*-butylamine **2a** were mixed in dichloroethane (DCE) and subjected to microwave irradiation to pre-form the corresponding Schiff base (Scheme 3). Addition of trifluoroethanol as solvent, the aryl-isocyanide **3a**, and $TMSN_3$ with stirring under ambient conditions afforded the condensation product in good isolated yield.[9] **8a** was treated with an excess of isocyanate **10a** in ethanol at ambient temperature and **9a** precipitated as a microcrystalline powder directly from the reaction mixture, isolated in a satisfactory 77% yield.[10] The structure of **9a** was unambiguously confirmed by X-ray crystallography (Fig. 1).

With satisfactory conditions in hand, the reaction scope in terms of substrate tolerance was explored. A small collection of 12 examples was prepared according to the same synthetic protocol (**9a–l**, Fig. 2). Seven amines (**2a–g**), six isonitriles (**3a–f**), six

* Corresponding author. Address: Department of Pharmacology and Toxicology, College of Pharmacy, BIO5 Oro Valley, The University of Arizona, 1580 E. Hanley Blvd., Oro Valley, AZ 85737, USA. Tel.: +1 520 626 5322.
E-mail address: hulme@pharmacy.arizona.edu (C. Hulme).

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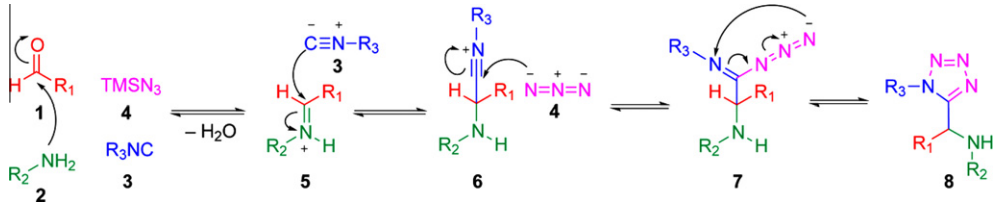
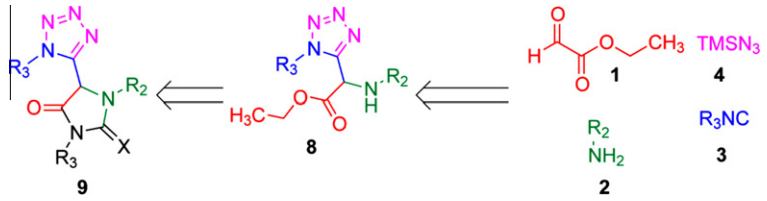
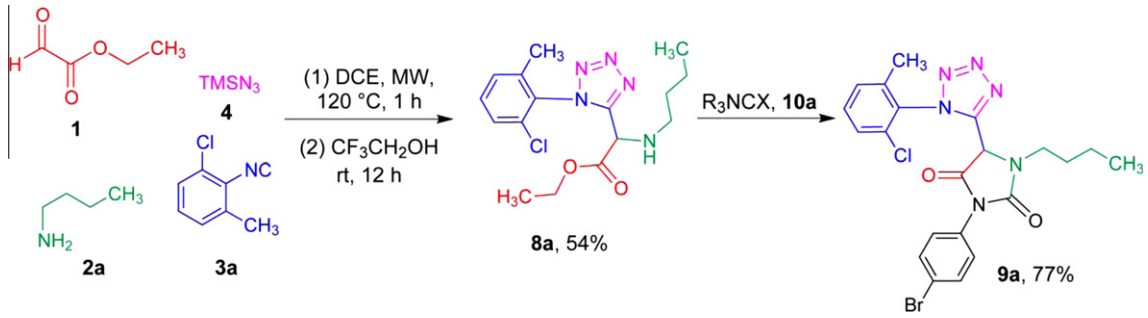


Scheme 1. Four-component $TMSN_3$-UGI reaction mechanism.



Scheme 2. Retrosynthetic analysis (X = O or S).



Scheme 3. Synthesis of **9a** via post-condensation modification of the $TMSN_3$-Ugi product **8a**.

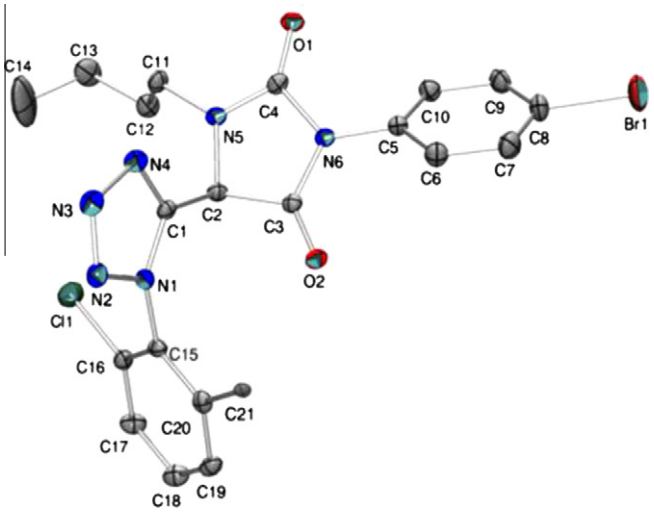


Figure 1. Crystal structure of **9a**.

isocyanates (**10a–f**), and one isothiocyanate (**10g**) were employed to impart significant diversity in the final collection of analogues. The $TMSN_3$-Ugi condensations afforded the desired condensation products in modest to high yields (**8a–i**, 21–60%) and generally, treatment of these products with an excess of isocyanate afforded the expected products **9a–j** in good to excellent yields (49–99%). Stoichiometry and conditions employed (room temperature vs. microwave irradiation, method A vs. method B, respectively) were optimal for different examples (Table 1). Target compounds **9a–f** formed smoothly at room temperature (49–77%), and further improvement was gained in the formation of bis-heterocyclics **9g–j** through the use of microwave irradiation at higher temperatures, affording **9g–j** in good yields (59–99%). Remarkably, most of the final products **9a–j** were formed as microcrystalline solids and easily isolated by suction filtration, thus greatly facilitating the production process.

Table 1
Optimization of the final cyclization reaction

Compound	R_3NCX (n equiv)	T (°C)	Time (h)	Method[a]
9a	4-Br-PhNCO (**10a**, 3)	rt	12	A
9b	4-F-PhNCO (**10b**, 6)	rt	36	A
9c	4-EtO-PhNCO (**10c**, 6)	rt	36	A
9d	PhNCO (**10d**, 2)	rt	24	A
9e	4-EtO-PhNCO (**10c**, 3)	rt	6	A
9f	4-EtO-PhNCO (**10c**, 3)	rt	2	A
9g	4-EtO-PhNCO (**10c**, 3)	120	1.5	B
9h	3-Me-PhNCO (**10e**, 6)	120	2	B
9i	EtNCO (**10f**, 3)	140	2	B
9j	PhNCO (**10d**, 6)	130	2	B
9k	TMSNCS (**10g**, neat)	180	2	B
9l	TMSNCS (**10g**, neat)	180	2	B

[a] Method A: EtOH, room temperature; Method B: EtOH, microwave irradiation.

Intrigued by the possibility to replace one of the carbonyl functional groups of the hydantoin core with a thio-carbonyl moiety, we employed neat TMSNCS for the production of **9k** and **9l**. Elevated temperatures generated by microwave irradiation enabled

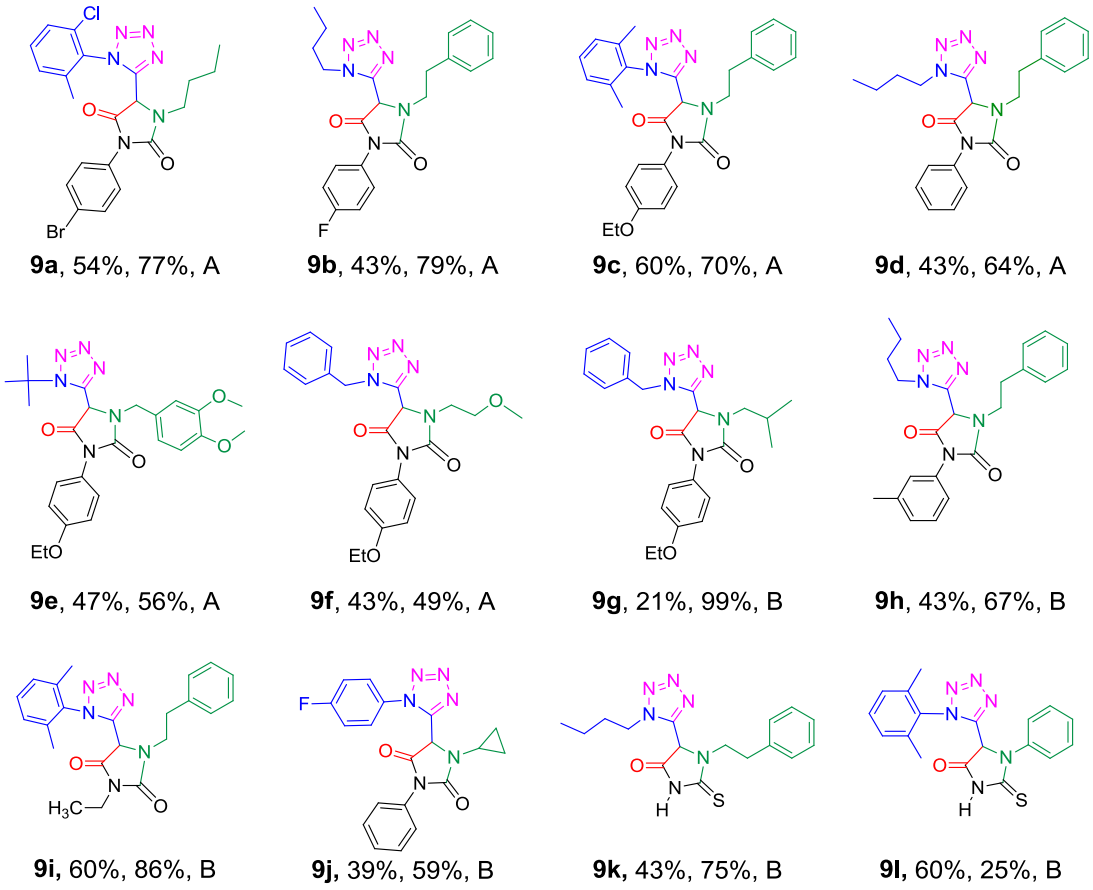


Figure 2. Example analogues (x% = $TMSN_3$-Ugi yield; y% = final cyclization yield; Z = method employed).

the formation of **9k** (75% yield), and **9l** (25% yield) respectively. The difference in the yields between **9k** and **9l** can be rationalized by the weaker nucleophilic character of the aniline-like $TMSN_3$-Ugi product **8l**.

In summary, a series of novel and biologically appealing 1,5-substituted tetrazole-hydantoins and thiohydantoins were prepared in two steps via rigidification of the $TMSN_3$-Ugi condensation product through treatment with an excess of isocyanates or isothiocyanate. Being characterized by four points of diversity, the novel chemotypes are rapidly assembled in two operationally friendly steps and the methodology proved to be general and tolerated a wide range of functional groups. Due to the potential biological activity of the novel scaffolds and the applicability of this methodology to high-throughput synthesis, we expect this article to be embraced by the lead generation community.

Acknowledgements

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10. General procedure for the preparation of **9a**: Ethyl glyoxalate (**1**, 50% solution in toluene, 1.1 g, 5.28 mmol, 1 equiv) and 1-butylamine (**2a**, 385 mg, 5.28 mmol, 1 equiv) were dissolved in DCE (10 mL) in a 35-mL vial and subjected to microwave irradiation at 120 °C for 1 h using a CEM initiator. CF_3CH_2OH (5 mL) was added, followed by azidotrimethylsilane (**4**, 610 mg, 5.28 mmol, 1 equiv) and 2-chloro-6-methyl-phenylisocianide (**3a**, 797 mg, 5.28 mmol, 1 equiv), and the resulting mixture was stirred at room temperature for 12 h. After removal of the solvent under reduced pressure, **8a** was purified by silica gel column chromatography (EtOAc–hexane, 0–30%) and isolated as a pale yellow oil (500 mg, 1.42 mmol, 54%). **8a** (250 mg, 0.80 mmol, 1 equiv) was dissolved in dry ethanol (2 mL) under a nitrogen atmosphere, 4-bromo-phenylisocyanate (**10a**, 474 mg, 2.40 mmol, 3 equiv) was added, and the reaction was stirred at room temperature for 12 h. The final product **9a** precipitated from the reaction mixture and was isolated by suction filtration as a white microcrystalline solid (220 mg, 0.43 mmol, 77%). Crystals suitable for X-ray crystal structure determination were obtained by means of slow evaporation from EtOAc–hexane. Mp 185–188 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58–7.39 (m, 5H), 7.28–7.24 (m, 2H), 5.24 (s, 1H), 3.92–3.85 (m, 1H), 3.24–3.16 (m, 1H), 2.22 (s, 3H), 1.58–1.54 (m, 2H), 1.35–1.33 (m, 2H), 0.92 (t, 3H, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.3 (C), 154.4 (C), 150.7 (C), 141.3 (C), 133.0 (CH), 132.6 (CH), 131.0 (CH), 130.9 (C), 130.4 (C), 129.7 (C), 128.1 (CH), 127.6 (CH), 122.7 (C), 54.7 (CH), 53.6 (CH_3), 42.5 (CH_2), 42.5 (CH_2), 29.9 (CH_2), 13.9 (CH_3); LC MS $[M+1]^+$ m/z 503.00.