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Facile Construction of Hydantoin Scaffolds *via* a Post-Ugi Cascade Reaction

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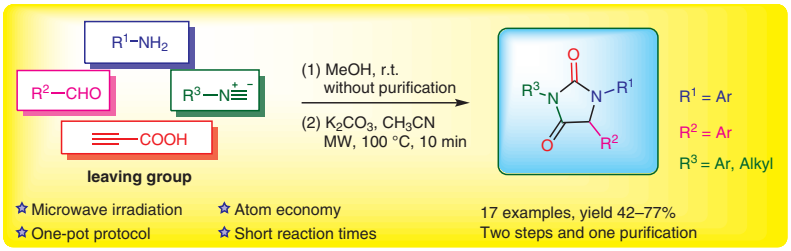

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Abstract A small series of hydantoins was efficiently synthesized *via* a two-step Ugi/cyclization reaction sequence using alkyne group as a leaving group under basic conditions. This microwave-assisted one-pot cyclization strategy could be applicable to other multicomponent reactions (MCRs) for synthesizing bioactive and drug-like hydantoins.

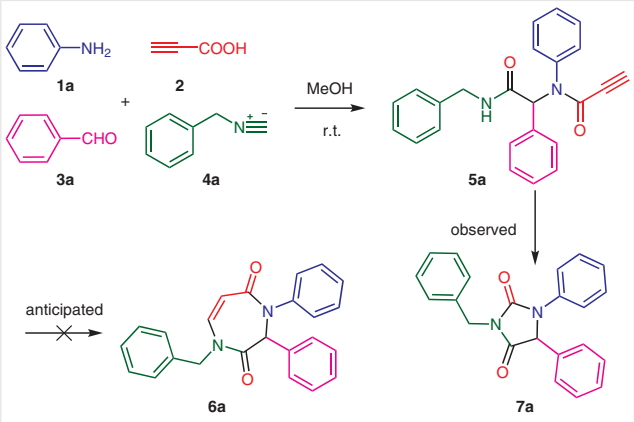
Key words hydantoins, multicomponent reactions (MCRs), one-pot, alkyne group, leaving group

Hydantoins, an important class of versatile compounds, has been widely investigated in medicinal and organic chemistry.[1] In recent years, the interest has been focused on pharmacological activities like androgen receptors,[2] perforin inhibitors,[3] $P2X_7$ receptor antagonists,[4] mutant IDH1 inhibitors,[5] antischistosomal,[6] CB1 cannabinoid receptor antagonists,[7] and antagonists of leukocyte cell adhesion acting as allosteric inhibitors.[8] Various different methods for the synthesis of hydantoins have been recently developed both in solution and in the solid phase to improve the drawbacks associated with reductive amination[9] or Mitsunobu reaction.[10] However, even if some of these methods allow the synthesis of hydantoins under milder conditions, less of them meet the modern requirements to be 'green' and 'practical', all of them being multistep procedures.

Multicomponent reactions (MCRs) have attracted considerable attention as powerful tools for the rapid construction of highly functionalized heterocyclic skeletons of chemical and biomedical importance.[11] Recently, privileged scaffolds represented by hydantoins were prepared via a MCR, an efficient three-component reaction, domino process for the synthesis of libraries of 1,3-disubstituted-5-arylhydantoins with a high degree of diversity starting from simple and easily accessible reactants.[12] Similarly, a structure of pseudopeptidic hydantoin was constructed through a diastereoselective synthesis of helix-forming by an Ugi/cyclization/Ugi sequence of reactions with trichloroacetic acid as a leaving group.[13] The cost-effective and environment-friendly conditions, short reaction steps, and simple workups would be still desirable.

We have a long-standing interest in the use of the Ugi cascade reaction for the formation of new C–C bonds as a general strategy for the construction of heterocycles for drug discovery.[14] In this regard, we were pleased to find that the results of our previous work provided us with a new opportunity to use propiolic acid, surprisingly to find it as a leaving group to synthesize a hydantoin core (Scheme 1).

Initially, to form the Ugi core, aniline (**1a**), propiolic acid (**2**), benzaldehyde (**3a**), and phenyl isonitrile (**4a**) were mixed in methanol with stirring overnight at room temperature to afford compound **5a** in excellent yield (Scheme 1). Unfortunately, on our first reaction conditions testing, the subsequent cyclization under thermal conditions in the presence of a base did not proceed to afford the anticipated product **6a**, but instead gave the unexpected hydantoin analogue **7a**. The structure of compound **7a** was unequivocally confirmed by the NMR data from a known compound and X-ray results (see Supporting Information).[15,16] The alkyne group was actually used as a leaving group in the



Scheme 1 Synthetic strategy of compounds **6a** and **7a**

ring-cyclization step. Although the leaving group of trichloroacetic acid has been reported to synthesize the hydantoins,[15] the alkyne group would enrich this synthesis method and can be applied to other synthetic processes.

Optimization work was therefore conducted to improve the yield of this reaction. To begin, we screened various bases of triethylamine (TEA), diisopropylamine (DIPA), *N*,*N*-diisopropylethylamine (DIPEA), and 4-dimethylaminopyridine (DMAP). Pleasingly, for all of the organic bases tested in this study, the hydantoin compound **7a** could be observed in 21–81% yield with microwave irradiation (Table 1, entries 1–5). Based on these good results, some inorganic bases were tested continually under microwave irradiation conditions. As expected, inorganic bases still could afford compound **7a** (Table 1, entries 6–15) with higher yields than those of organic bases, but KOH did not afford compound **7a** in good yield (Table 1, entries 7–10). It is noteworthy that the microwave irradiation at 100 °C in CH_3CN for 20 min could afford the desired product **7a** in 93% yield. Gratifyingly, we also investigated the effect of the reaction time, solvents, and equivalent of K_2CO_3 and found that the optimized reaction conditions are (Table 1, entry 20) heating the reaction mixture at 100 °C under microwave irradiation for 10 min in CH_3CN. The synthesis of compound **7a** was tracked by the HPLC following these conditions (see Supporting Information for details). Notably, switching the solvent to DMSO, DMF, ethanol, or 1,4-dioxane led to the lower yields of compound **7a** (Table 1, entries 21–24).

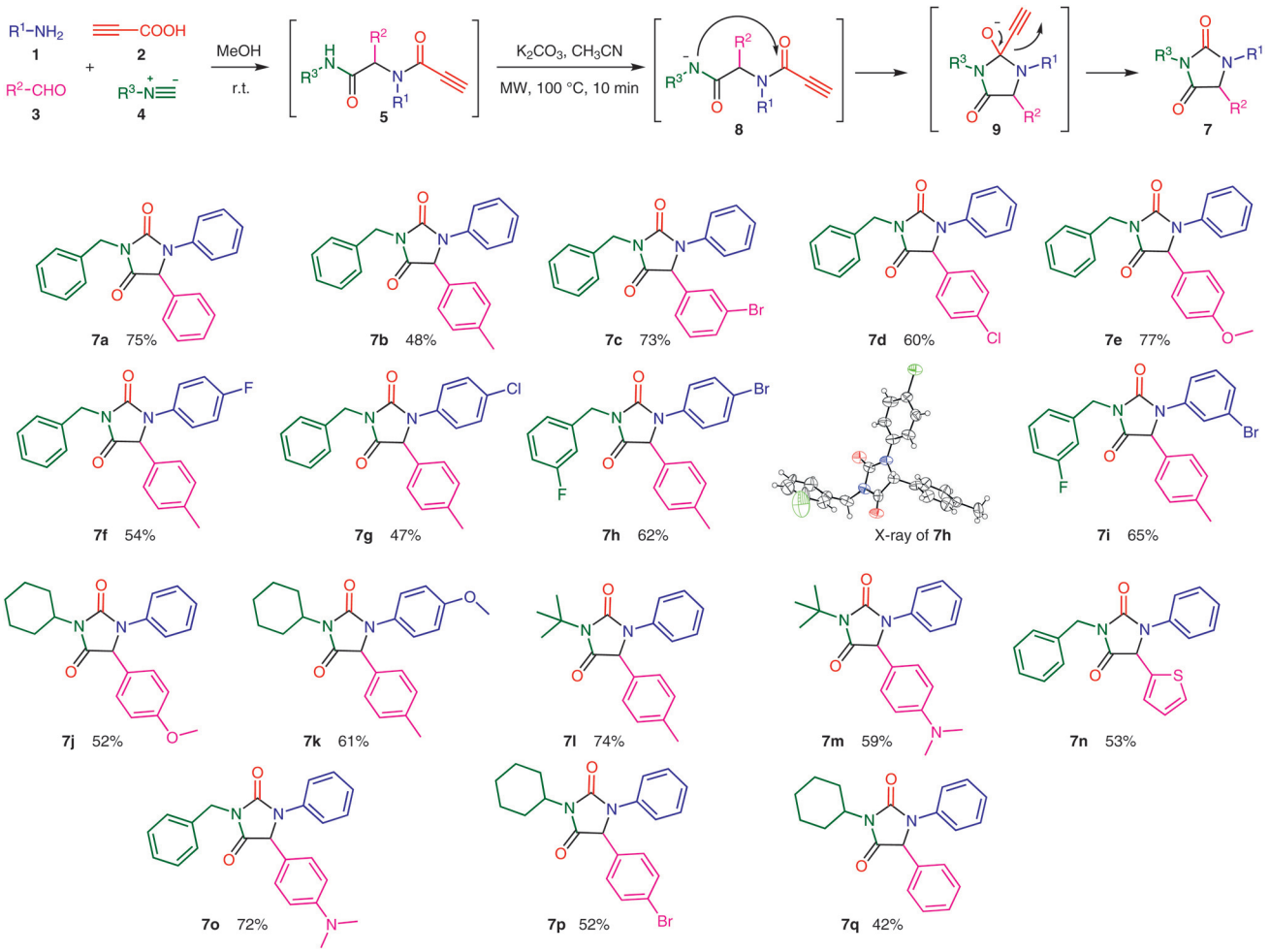
Table 1 Optimization of the Reaction Conditions for the Synthesis of **7a**

Entry	Base	Solvent	Time (min)MW	Temp (°C)	Yield (%)[a]
1	TEA (2 equiv)	CH_3CN	20	140	81
2	DIPA (2 equiv)	CH_3CN	20	140	21
3	DIPEA (2 equiv)	CH_3CN	20	140	73
4	DMAP (2 equiv)	CH_3CN	20	140	72
5	DBU (2 equiv)	CH_3CN	20	140	62
6	NaOEt (2 equiv)	CH_3CN	20	140	65
7	KOH (1 equiv)	CH_3CN	10	90	42
8	KOH (1 equiv)	CH_3CN	10	100	37
9	KOH (1 equiv)	CH_3CN	10	110	9
10	KOH (2 equiv)	CH_3CN	20	140	NR
11	Na_2CO_3 (2 equiv)	CH_3CN	20	140	80
12	Cs_2CO_3 (2 equiv)	CH_3CN	20	140	85
13	KOAc (2 equiv)	CH_3CN	20	140	72
14	KF (2 equiv)	CH_3CN	20	140	77
15	K_2CO_3(2 equiv)	CH_3CN	20	100	93
16	K_2CO_3(2 equiv)	CH_3CN	20	80	60
17	K_2CO_3(2 equiv)	CH_3CN	20	90	84
18	K_2CO_3(2 equiv)	CH_3CN	10	100	93
19	K_2CO_3 (0.5 equiv)	CH_3CN	10	100	46
20	K_2CO_3 (1.0 equiv)	CH_3CN	10	100	94
21	K_2CO_3(1 equiv)	DMSO	10	100	21
22	K_2CO_3(1 equiv)	DMF	10	100	70
23	K_2CO_3(1 equiv)	EtOH	10	100	40
24	K_2CO_3 (1 equiv)	Diox	10	100	37

[a] Yield (%) based on peak area of the product by HPLC analysis at 254 nm.
MW = microwave.

Encouraged by the remarkable yield at the optimized conditions, we investigated the scope of this cyclization by varying starting materials. Propiolic acid (**2**) was treated with various substituted isonitriles, amines, and benzaldehydes in methanol at room temperature overnight to give the crude Ugi product **5**, which was directly subjected to cyclization reaction after the removal of solvent under a gentle stream of nitrogen. Then, under the basic conditions, following the intermediates **8** and **9**, nucleophilic addition and elimination reactions occurred to give product **7**. A variety of different starting materials were successfully employed under the optimized conditions for the construction of structurally diverse hydantoin **7a–q** with yields of 42–77% (Scheme 2), indicating a good functional group tolerance. It is noteworthy that the products of the Ugi reaction did not require purification by column chromatography, with the crude products having no discernible impact on the overall yield. The results further confirm the utility and the potential broad application of this novel methodology.

In summary, we have developed an unprecedented post-Ugi cascade reaction in one-pot for the construction of highly functionalized hydantoins, which are important pharmacophores and privileged structures that can be found in many biologically important compounds in medicinal chemistry. The cascade cyclization using the leaving property of alkyne group with the microwave irradiation under basic conditions design approach would be highly



Scheme 2 Scope of the Ugi cascade reaction route leading to hydantoin **7a–q**.

applicable to other MCRs such as Passerini,[17] Petasis,[18] Betti,[19] Kabachnik–Fields,[20] Mannich[21], etc. This new method[22] for the construction of complex heterocyclic systems could provide a platform for the further diversification of hydantoin scaffolds and studies on their potent biological activity.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610234.

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(22) **General Procedure for the Preparation of Hydantoin Compound 7**

A solution of aniline (1.0 mmol), propiolic acid (1.0 mmol), benzaldehyde (1.0 mmol), and isonitrile (1.0 mmol) were mixed in methanol with stirring overnight at room temperature. The reaction mixture was monitored by TLC. When no isonitrile was left, the solvent was removed under a gentle stream of nitrogen. Then, the residue was diluted with CH_3CN (5.0 mL) and K_2CO_3 (1.0 mmol) was added. The reaction mixture was treated in microwave at 100 °C for 10 min. After the microwave vial was cooled to room temperature, the reaction mixture was diluted with EtOAc (25 mL) and washed with water and brine. Then the organic layer was dried with Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography using a gradient of EtOAc/hexane (15–30%) to afford the relative targeted product **7**.

Analytical Data for Compound **7a**White solid, 75%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.71–4.83 (q, *J* = 14.4 Hz, 2 H), 5.46 (s, 1 H), 7.05–7.09 (t, *J* = 7.6 Hz, 1 H), 7.23–7.27 (m, 2 H), 7.27–7.35 (m, 8 H), 7.43–7.47 (t, *J* = 8.8 Hz, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.59, 160.24, 154.41, 136.47, 135.75, 134.35, 130.37, 129.11, 128.74, 128.07, 124.75, 120.20, 119.01, 114.73, 112.21, 64.26, 42.90. HRMS (ESI): *m/z* calcd for $C_{22}H_{18}N_2O_2^+$ [M + H]$^+$: 343.14465; found: 343.14431.