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Rapid access to conformationally-constrained oxatricycles via Ugi-Smiles couplings

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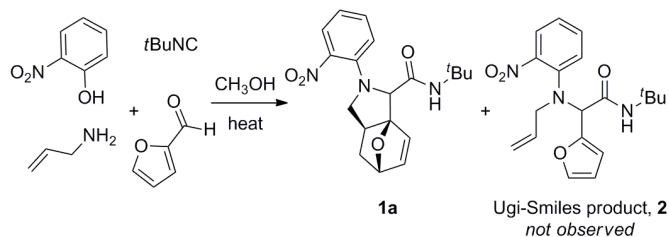
ABSTRACT

Use of allylamine and substituted 2-furaldehydes as components in Ugi-Smiles couplings of 2-nitrophenol provide ready access to *N*-aryl epoxyisoindolines. These adducts form via a dual event involving the Ugi-Smiles multicomponent reaction and an intramolecular Diels-Alder cycloaddition with the furan ring.

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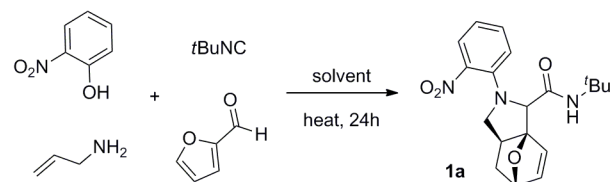
The Ugi four-component reaction¹ provided a foundation for the development of novel isocyanide-based multicomponent reactions (IMCRs)² to efficiently access heterocyclic scaffolds.³ A particularly useful modification of these foundational IMCRs was reported as the Ugi-Smiles reaction by El Kaïm and coworkers,^{4,5} in which electron-deficient phenols serve as surrogates for the standard carboxylic acid components. The Ugi-Smiles reaction has been reported in one-pot cascade processes with Sonogashira couplings,⁶ acidic cyclizations,⁷ palladium-catalyzed deallylations,⁸ and copper-triggered oxidative cycloadditions⁹ to prepare diverse heterocyclic libraries.

One notable limitation of the reported Ugi-Smiles reaction is the lack of reactivity observed for use of α,β -unsaturated aldehydes or 2-furaldehyde as components.^{10,11} While the classical Ugi and Passerini reactions tolerate these aldehyde components,¹² the analogous Ugi-Smiles reactions are generally unsuccessful.¹³



Scheme 1. *N*-Aryl epoxyisoindolines via Ugi-Smiles/IMDA

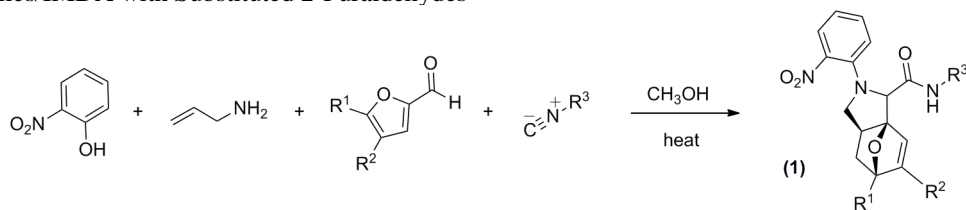
Table 1 Comparison of solvents for Ugi-Smiles/IMDA^a



Entry	Solvent	Temperature	Yield (%) ^b
1	CF ₃ CH ₂ OH	60 °C	21
2	CH ₃ OH	60 °C	52
3	CH ₃ OH	100 °C, sealed tube	40
4	H ₂ O	60 °C	53
5	CH ₃ CN	60 °C	26
6	Toluene	60 °C	8
7	neat	60 °C	50

^a Standard reaction (0.5 mmol, 1.0 M) performed with 2.0 equiv *tert*-butyl isocyanide. ^b Isolated yields represent the sum of the two diastereomers obtained after products were separated via column chromatography.

We were interested in exploring 2-furaldehyde and allylamine as the respective aldehyde and amine components in an Ugi-Smiles coupling, providing a system amenable for cascade with an intramolecular Diels-Alder reaction, to directly prepare conformationally-constrained oxatricycles.¹⁴ Successful IMDA reactions with a furan diene (IMDAF) have been reported

Table 2 Ugi-Smiles/IMDA with Substituted 2-Furaldehydes^a

Entry	R ¹	R ²	R ³	Time / Temp	Product	Yield (%) ^b
1	H	H	<i>tert</i> -Butyl	24 h / 60 ° C	1a	52
2	Cl	H	<i>tert</i> -Butyl	24 h / 60 ° C	1b	34
3	Br	H	<i>tert</i> -Butyl	24 h / 60 ° C	1c	43
4	I	H	<i>tert</i> -Butyl	24h / 60 ° C	1d	48
5	CH ₃	H	<i>tert</i> -Butyl	42 h / 60 ° C	1e	49
6	CH ₃	CH ₃	<i>tert</i> -Butyl	30 h / 50 ° C	1f	42
7	H	Br	<i>tert</i> -Butyl	30 h / 50 ° C	1g	56
8	H	H	Cyclohexyl	24 h / 60 ° C	1h	68
9	Br	H	Cyclohexyl	30 h / 50 ° C	1i	60/42 ^c
10	I	H	Cyclohexyl	30 h / 50 ° C	1j	59/50 ^c
11	CH ₃	H	Cyclohexyl	30 h / 50 ° C	1k	60/48 ^c
12	CH ₃	CH ₃	Cyclohexyl	30 h / 50 ° C	1l	51 ^c

^a Standard reaction performed with 2.0 equiv isocyanide in methanol (1.0 M). ^b Only *exo*-adduct observed. Both diastereomers at α -amino amide carbon observed. Isolated yields represent the sum of the two diastereomers (~1:1 dr) obtained after products were separated via column chromatography; see Supporting Information for details. ^c Performed with 1.0 equiv isocyanide, 30 h, 50 °C.

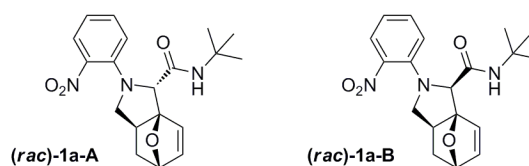
extensively for systems with tethered furanylamides,¹⁵ alkenyl furfurylamines,¹⁶ or in sequence with an Ugi or Passerini MCR,¹⁷ leading to formation of diverse oxabicyclo[2.2.1] systems.¹⁸

Herein, we report an efficient Ugi-Smiles coupling/intramolecular Diels-Alder cycloaddition (US/IMDA) with 2-furaldehyde, which provides direct access to *N*-aryl epoxyisindoline **1a** through a simple, one-pot reaction (Scheme 1). Notably, no lone Ugi-Smiles adducts (**2**) were isolated for any reactions that used 2-furaldehyde. The remainder of recovered mass consisted of unreacted phenol and imine, formed *in situ* from 2-furaldehyde and allylamine. In the absence of a competent dienophile component, using aliphatic amines, no significant Ugi-Smiles coupled products were observed by ¹H NMR monitoring.

Methanol or toluene are the preferred solvents for Ugi-Smiles reactions, although water has also been used at elevated temperatures.¹⁹ Several solvents were screened for the dual Ugi-Smiles/IMDA process (Table 1),²⁰ including toluene, acetonitrile, water, and trifluoroethanol. Yields decreased as aprotic solvents were examined. Water, methanol, and solvent-free conditions provided comparable yields. Lower product conversion was observed when heating in methanol at an elevated temperature (100 °C) in a sealed Schlenk tube (entry 3). Diastereomeric ratios for products **1a** (A:B) were always close to 1:1. Relative amounts of the diastereomers and absence of Ugi-Smiles product (**2**) were supported by ¹H NMR spectra of the crude reaction mixtures and confirmed by isolated yields. Based on these solvent studies, methanol was used to examine the scope of the reaction with substituted 2-furaldehydes.

Oxatricyclic isindoline **1a** is the *exo* isomer²¹ produced by intramolecular Diels-Alder reaction of the furan and allyl

moieties. Two diastereomeric *exo* adducts were readily separable by column chromatography. Relative stereochemical determination by ¹H NMR, NOESY correlations, and X-ray crystallographic analysis identified the less polar diastereomer (**1a-A**) having the amide moiety on the opposite side of the ring system from the oxygen bridge while the more polar diastereomer (**1a-B**) has the amide moiety on the same side as the oxabridge (Figure 1).

**Figure 1.** Relative stereochemistry of **1a-A** and **1a-B**

We probed the scope of this reaction with several substituted 2-furaldehyde components (Table 2). Couplings with allylamine, 2-nitrophenol, and substituted 2-furaldehydes that included cyclohexyl isocyanide or *tert*-butyl isocyanide were successful, with two diastereomeric *exo* products isolated in moderate to good yields for each synthetic variation. 5-Halo-substituted 2-furaldehydes (entries 2-4, 9 and 10) and alkyl 2-furaldehydes (entries 5-6, 11 and 12) were competent partners for this process. Use of 4-bromo-2-furaldehyde (entry 7) also provided the expected US/IMDA product. Notably, use of electron-rich 5-methoxy-2-furaldehyde or electron-poor 5-nitro-2-furaldehyde as the aldehyde component provided no observed Ugi-Smiles or Ugi-Smiles/IMDA products.

Due to volatility concerns for allylamine, several reactions were performed at slightly reduced temperatures (50 °C). Equimolar amounts of the four components provide oxatricyclic isoindoline **1**, although increased yields were observed with the use of excess isocyanide. For reactions involving cyclohexyl isocyanide as a component, this increase in yield was accompanied by the formation of 1-allyl-3-cyclohexylurea, from the side reaction of cyclohexyl isocyanide and allyl amine. While product yields were improved with excess cyclohexyl isocyanide compared to equimolar reactions, difficult purifications accompanied these attempts, as the urea byproduct was similar in polarity to the less polar diastereomer (**1-A**).

In conclusion, this work offers the first examples of successful four-component Ugi-Smiles derived couplings with conjugated, heterocyclic aldehydes. *N*-aryl epoxyisoindoline structures are efficiently assembled from simple starting materials with points of diversity on the furan ring, providing straightforward access to conformationally-restricted oxatricyclic building blocks. We are currently extending these studies to examine alternate compatible dienophile components for this process.

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Supplementary data

Supplementary data (complete experimental procedures and product characterization data) associated with this article can be found, in the online version, at ...

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1a-A: *R*_f = 0.50 (50% ethyl acetate/hexanes); ¹H NMR (300 MHz, CDCl₃) δ 7.73 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.49-7.44 (m, 2H), 7.28 (d, *J* = 8.3 Hz, 1H), 7.07 (dd, *J* = 7.9, 7.9 Hz, 1H), 6.43 (d, *J* = 5.9 Hz, 1H), 6.40 (dd, *J* = 5.9, 1.6 Hz, 1H), 5.06 (dd, *J* = 4.4, 1.5 Hz, 1H), 4.55 (s, 1H), 3.78 (dd, *J* = 8.4, 8.4 Hz, 1H), 2.74 (dd, *J* = 9.6, 9.6 Hz, 1H), 2.25-2.16 (m, 1H), 1.78-1.71 (m, 1H), 1.46 (dd, *J* = 11.6, 7.6 Hz, 1H), 1.31 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 168.6, 142.7, 142.0, 136.5, 134.1, 130.6, 125.9, 122.4, 121.8, 97.2, 80.1, 65.9, 58.1, 51.3, 42.1, 30.9, 28.7; HR-FAB MS [M+Na]⁺ calcd for C₁₉H₂₃N₃NaO₄ 380.1586; found 380.1594.
1a-B: *R*_f = 0.27 (50% ethyl acetate/hexanes); ¹H NMR (300 MHz, CDCl₃) δ 7.77 (d, *J* = 8.2 Hz, 1H), 7.41 (dd, *J* = 8.6, 8.6 Hz, 1H), 7.05 (d, *J* = 8.3 Hz, 1H), 7.00 (dd, *J* = 7.7, 7.7 Hz, 1H), 6.56-6.43 (m, 3H), 5.15 (dd, *J* = 4.5, 1.6 Hz, 1H), 4.80 (s, 1H), 3.45 (dd, *J* = 9.8, 9.8 Hz, 1H), 3.01 (dd, *J* = 9.1, 9.1 Hz, 1H), 2.22-2.12 (m, 1H), 1.89-1.82 (m, 1H), 1.46-1.39 (m, 1H), 1.19 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 166.5, 141.7, 139.0, 137.9, 134.0, 133.4, 126.4, 118.8, 116.4, 95.6, 80.8, 64.4, 58.2, 51.3, 42.7, 31.4, 28.5; IR (KBr [cm⁻¹]): 3386 (m) [N-H], 3054 (m) [C-H], 1678 (s) [C=O], 1265 (s) [C-O], 739 (s) [C-N]; HR-FAB MS [M+H]⁺ calcd for C₁₉H₂₄N₃O₄ 358.1767; found 358.1760.
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