

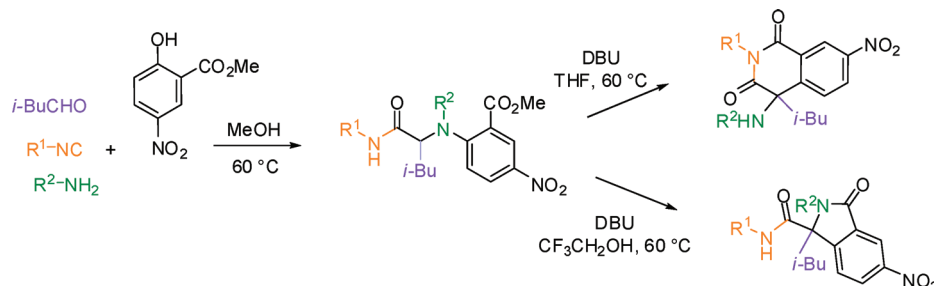
Smiles Cascades toward Heterocyclic
ScaffoldsLaurent El Kaim,^{*,†} Laurence Grimaud,^{*,†} Xavier F. Le Goff,[‡] and Aurélie Schiltz[†]

Laboratoire Chimie et Procédés, Ecole Nationale Supérieure de Techniques Avancées,
32 Bd Victor, 75739 Paris Cedex 15, France, and Laboratoire Hétéroéléments et
Coordination, Ecole Polytechnique, CNRS, Route de Saclay,
F-91128 Palaiseau Cedex, France

laurent.elkaim@ensta-paristech.fr; laurence.grimaud@ensta-paristech.fr

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ABSTRACT

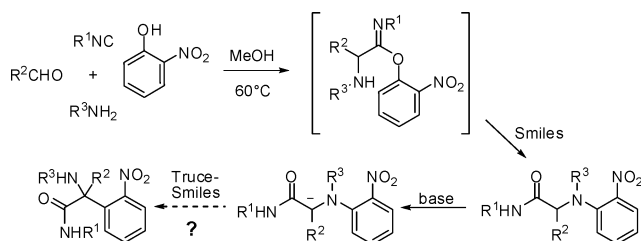


Two different Smiles rearrangements can be combined to afford a multicomponent formation of isoquinolinones and isoindolinones from nitro methyl salicylate. After a Ugi–Smiles four-component coupling, the base-triggered cyclization of the resulting adduct is followed by a ring contraction via a Truce–Smiles rearrangement.

The Smiles rearrangements consist of an intramolecular migration of aromatic rings between two nucleophilic centers.¹ The presence of electron-withdrawing groups on the aromatic ring ensures the efficiency of the interaction with the nucleophiles, which are most often based on heteroatoms such as N, O, or S. However, in the Truce–Smiles rearrangement, a nucleophilic carbon is involved, leading to new carbon–carbon bond formation.²

A few years ago, we reported a four-component Ugi-type coupling with electron-deficient phenols (Scheme 1).³ The

Scheme 1. Envisioned Smiles Cascades



reaction features as the key step of an efficient Smiles rearrangement controlled by the conversion from an imide to an amide conversion. Since this report, we have contemplated using these Ugi–Smiles adducts in further Truce–Smiles reactions (Scheme 1).

Beside the attraction of performing a cascade of Smiles rearrangements, we felt that the synthetic strategy of creating an intermediate N-aryl compound to form the final C-aryl

[†] Ecole Nationale Supérieure de Techniques Avancées.[‡] Ecole Polytechnique, CNRS.

(1) (a) Levy, A. A.; Rains, H. C.; Smiles, S. *J. Chem. Soc.* **1931**, 3264. For reviews see: (b) Bunnet, J. F.; Zaller, R. E. *Chem. Rev.* **1951**, 49, 273–308. (c) Truce, W. E.; Kreider, E. M.; Brand, W. W. *Org. React. (N. Y.)* **1970**, 18, 99–215. (d) Plesniak, K.; Zarecki, A.; Wicha, J. *Top. Curr. Chem.* **2007**, 275, 163–250.

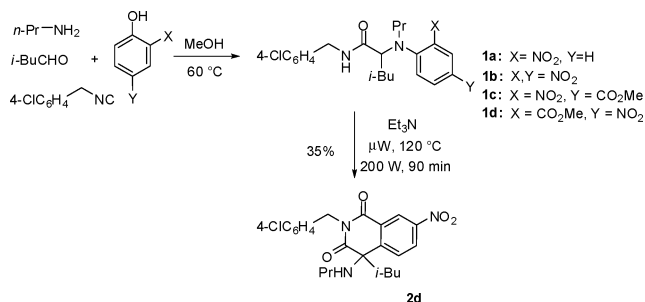
(2) (a) Truce, W. E.; Ray, W. J., Jr.; Norman, O. L.; Eickemeyer, D. B. *J. Am. Chem. Soc.* **1958**, 80, 3625–3629. For a review, see: (b) Snape, T. J. *Chem. Soc. Rev.* **2008**, 37, 2452–2458.

(3) (a) El Kaim, L.; Grimaud, L.; Oble, J. *Angew. Chem., Int. Ed.* **2005**, 44, 7165–7169. El Kaim, L.; Gizolme, M.; Grimaud, L.; Oble, J. *J. Org. Chem.* **2007**, 72, 4169–4180.

bond held tremendous appeal, since to create directly such a carbon-aryl bond intermolecularly would be far more difficult. We recently reported various deprotonations of the CH peptidic position of Ugi–Smiles adducts leading to carbon–carbon bond formations.⁴ Using these anions in Truce–Smiles reactions was rather challenging, as this project would imply a 3-*exo*-trig cyclization, whereas most Smiles rearrangements feature 5-*exo*-cyclizations.⁵

The Ugi–Smiles adduct **1a** obtained from propyl amine, isovaleraldehyde, 4-chlorobenzylisocyanide, and 2-nitrophenol failed to give any Truce–Smiles rearranged products under a set of basic conditions. In the search for more electrophilic aromatic rings, we next examined the behavior of adducts **1b–1d** derived from 2,4-dinitrophenol, methyl 4-hydroxy-3-nitro-benzoate, and methyl 4-nitro-salicylate, the latter being of further interest due to potential cyclizations onto the ester moiety. Though different basic conditions failed to give any reaction with adducts **1b** and **1c**, an interesting transformation was observed when salicylate derivative **1d** was treated under microwave irradiation in triethylamine as solvent. Indeed, the formation of isoquinolinone **2d** in a moderate 35% isolated yield revealed a quaternarized peptidic position with the carbon directly linked to the aromatic core, which could be explained by a Truce–Smiles rearrangement (Scheme 2).

Scheme 2. First Truce–Smiles Rearrangement



Encouraged by this first result, different sets of conditions were next investigated to optimize such a reaction as displayed in Table 1.

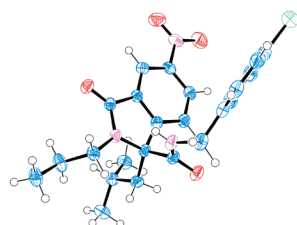
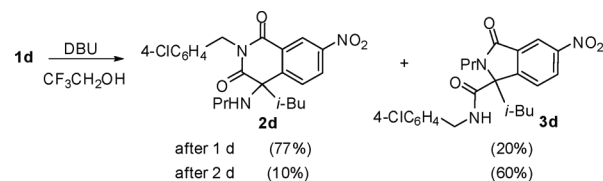
The best conditions were obtained when using a large excess of base, at least 5 equiv of DBU (Table 1, entries 6–8) or NaH (Table 1, entry 3), in a polar solvent such as THF (Table 1, entry 7) or DMF (Table 1, entry 3) or a polar protic solvent such as CF₃CH₂OH (Table 1, entries 8). However, when using DBU in 2,2,2-trifluoroethanol, the desired isoquinolinone **2d** was isolated along with 20% of the isoindolinone **3d** (Scheme 3).

Table 1. Optimization of the Reaction Conditions

entry	base(equiv)	solvent	temperature(time)	yield
1	<i>t</i> -BuOK (1.2)	THF	80 °C (3 d)	nr ^a
2	NaH (1.2)	DMF	100 °C (4 d)	nr
3	NaH (5)	DMF	100 °C (3 d)	43%
4	DBU (1.2)	MeCN	80 °C (3 d)	nr
5	DBU (1.2)	1,2-DCE	80 °C (3 d)	nr
6	DBU/1,2-DCE (1:1)		80 °C (2 d)	53%
7	DBU (5)	THF	60 °C (1 d)	65%
8	DBU (5)	CF ₃ CH ₂ OH	60 °C (1 d)	77%

^a nr: no reaction.

Scheme 3. Behavior of **1d** in Protic Solvents



X-ray structure for **3d**

The structure of byproduct **3d** was confirmed by an X-ray analysis (Scheme 3).⁶ Though **3d** might result from a direct Truce–Smiles rearrangement followed by a cyclization, a time/ratio dependence is more in favor of a formation of **3d** through rearrangement of isoquinolinone **2d**. This last observation led us to propose a set of two conditions for the formation of either isoquinolinone **2** or isoindolinone **3** according to the solvent used in the reaction. Thus, various Ugi–Smiles adducts were treated with an excess of DBU in THF and 2,2,2-trifluoroethanol at 60 °C to form the corresponding isoquinolinones **2** and isoindolinones **3** as listed in Table 2.

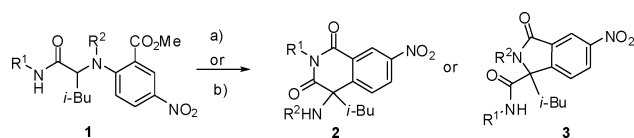
The results depicted above indicate a strong influence of the bulkiness of the isocyanide and aldehyde on the fate of the reaction. When cyclohexyl and *tert*-butyl isocyanides

(4) (a) El Kaim, L.; Gamez-Montano, R.; Grimaud, L.; Ibarra-Rivera, T. *Chem. Commun.* **2008**, 1350–1352. (b) El Kaim, L.; Grimaud, L.; Wagschal, S. *J. Org. Chem.* **2010**, 75, 5343–5346.

(5) (a) For a possible Smiles rearrangement of *N*-aryl sulfonamide involving a three-membered spiro intermediate, see: Muller, P.; Phuong, N.-T. M. *Helv. Chim. Acta* **1979**, 62, 494–496.

(6) The crystallographic data can be obtained free of charge under the reference CCDC 801186 at the Cambridge Crystallographic Data Centre (www.ccdc.cam.ac.uk/data_request_cif).

(7) A related Truce–Smiles rearrangement was already observed in a Ugi cyclic adduct (Dai, W.-M. Book of Abstracts, IV International Conference on Multi-component Reactions and Related Chemistry (MCR2009), Ekaterinburg, Russia, 24–28 May 2009, p 14).

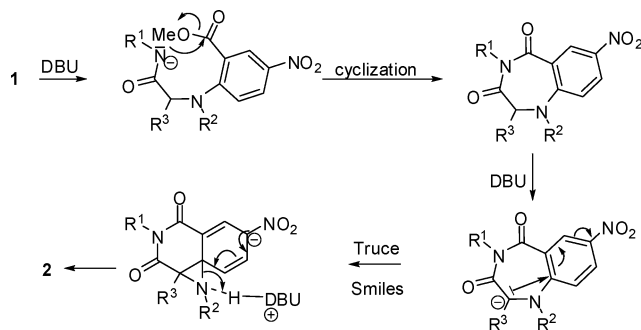
Table 2. Scope of the Cyclization–Truce–Smiles Cascades

entry	R ¹	R ²	1 ^a (yield)	2 ^b (yield)	3 ^c (yield)
1	<i>t</i> -Bu	<i>n</i> -Pr	1e (38%)	nr	nr
2	Cy	<i>n</i> -Pr	1f (67%)	4f (53%)	
3	4- <i>t</i> -BuC ₆ H ₄ CH ₂	<i>n</i> -Pr	1g (53%)	2g (43%)	3g (36%)
4	4-MeOC ₆ H ₄ CH ₂	<i>n</i> -Pr	1h (57%)	2h (54%)	3h (59%)
5	CH ₂ =CH-CH ₂	<i>n</i> -Pr	1i (23%)	2i (37%)	3i (48%)
6	3,4-MeOC ₆ H ₃ CH ₂	<i>n</i> -Pr	1j (66%)	2j (50%)	3j (54%)
7	4- <i>t</i> -BuC ₆ H ₄ CH ₂	(CH ₂) ₂ OMe	1k (47%)	2k (52%)	3k (50%)
8	4- <i>t</i> -BuC ₆ H ₄ CH ₂	4-ClBn	1l (42%)	2l^b (35%)	3l (21%)

^a Isolated yield for the synthesis of **1**. ^b Isolated yields for **2** using DBU (5 equiv) in THF at 60 °C. ^c Isolated yields for **3** using DBU (10 equiv) in CF₃CH₂OH at 60 °C.

were used, the corresponding isoquinolinones and isoindolinones could not be obtained (Table 2, entries 1–2). In the case of aldehydes, these cyclizations could not be observed with an aromatic substituent probably due to the higher stability of the peptidyl enolate.

With all these results in hand, the obtention of **2d** may be understood by a sequence of events involving a cyclization of the amide onto the ester moiety, followed by a Truce–Smiles rearrangement (Scheme 4). The timing of this sequence is confirmed by the lack of reactivity of **1e** and **1f**

Scheme 4. Plausible Mechanism

(Table 2, entries 1–2). For the reactant **1e**, the cyclization to an intermediate benzodiazepinedione is either impossible or disturbed by the steric hindrance of the *tert*-butyl group. The results obtained from cyclohexyl isocyanide adduct **1f** further confirm this cyclization path. In this case, most surprisingly, the intermediate benzodiazepinedione **4f** failed to undergo the Truce–Smiles rearrangement, suggesting a strong dependence on the conformation of the cyclic intermediates. Final conversion of **2d** into **3d** may be explained by an intramolecular addition of the amino residue onto the imide with subsequent release of an amido group.

In conclusion, we have reported a new isocyanide-based multicomponent sequence toward isoquinolinones and isoindolinones. The strategy implies a series of Smiles rearrangements allowing the formation of scaffolds, which are unusual in IMCR-based synthesis. The interest of the sequence is further enhanced by the Truce–Smiles rearrangement involved. Indeed, its mechanism involves [3,6]-spiro species which is unprecedented in the literature.⁷ Mechanistic calculations are currently being studied to gain more insight into this transformation.

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Supporting Information Available: Experimental procedures and spectral data for new compounds are detailed. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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