Allyl and Benzyl Dance under Basic Conditions

Laurent El Kaim,* Laurence Grimaud,* Srinivas Reddy Purumandla

Laboratoire Chimie et Procédés, UMR 7652, Ecole Polytechnique-ENSTA-CNRS, Ecole Nationale Supérieure de Techniques Avancées, 32 Bd Victor, 75739 Paris Cedex 15, France
Fax +33(1)45528322; E-mail: laurent.elkaim@ensta.fr; E-mail: grimaud@dcso.polytechnique.fr
Received 9 May 2011

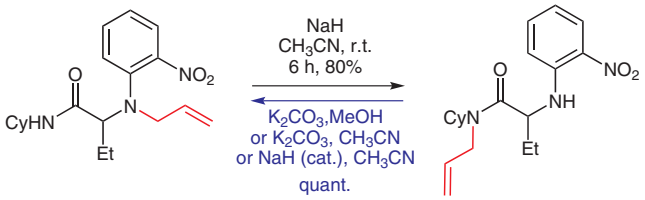
Abstract: Ugi–Smiles adducts formed from allyl (propargyl or benzyl) amine rearrange under basic condition with an allyl migration between two nitrogen atoms. The shift is reversible and may be controlled by the strength of the base used in the reaction.

Key words: Ugi–Smiles, isocyanide, multicomponent couplings, allyl, benzyl, propargyl, migration

A few years ago, we disclosed a new Ugi-type coupling involving electron-deficient phenols.[1] This transformation was coined as the Ugi–Smiles coupling in relation with the rerrangement involved in the process. It converts the isocyanide component into a secondary carboxamide as observed in most Ugi couplings (Scheme 1). We wish to disclose herein a novel base-induced rearrangement involving the amide functionality of Ugi–Smiles adducts.

Following our initial report on these couplings, we explored the reactivity of the new Ugi–Smiles adducts and disclosed various syntheses of fused heterocycles.[2] During these studies, we became particularly interested by the trapping of the potential anions resulting from a basic treatment of the products. Indeed, two positions may be subject to deprotonation, the N–H amide and the peptidyl C–H. With aromatic aldehydes, the peptidyl position becomes more acidic and the anion, formed under DBU treatment, may be trapped intramolecularly.[3] With aliphatic aldehydes, the functionalization of the peptidyl position requires the use of a strong base in excess due to the higher acidity of the amide moiety.[4] While working on these topics, we observed with the *N*-allyl Ugi–Smiles product **1a** a shift of the allyl group forming **2a** under treatment with a slight excess of sodium hydride in acetonitrile at room temperature (Scheme 1). Such migration, rather unusual for Ugi-type adducts, could be explained by the formation of a highly stabilized aniline anion.

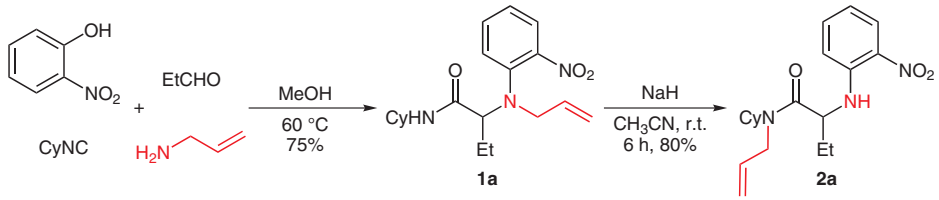
With such an easy rearrangement, we surmised that new heterocyclic systems could be prepared from **2a** through N-alkylation. However, when treating **2a** with various alkylating agents in methanol with potassium carbonate as a base, we unexpectedly recovered **1a** within a few hours at room temperature. The same result was obtained in the absence of alkylating agent, and **1a** was isolated in quantitative yield. To our surprise, such a shift was also observed in acetonitrile as solvent with potassium carbonate or using a catalytic amount of sodium hydride (Scheme 2). The nature of this 'allyl dance'[5] was very puzzling, and we decided to study its scope and mechanism.



Scheme 2 'Allyl dance' under basic conditions

Using various amine partners in the Ugi–Smiles process, we first confirmed that, with a simple alkyl chain such as a methoxy ethyl group, nothing happened under basic conditions (Table 1, entry 1). However, the allyl group migrates for a set of different partners in the four-component reaction (Table 1, entries 2–4). The propargyl and benzyl groups demonstrated migratory abilities as well (Table 1, entries 5–7).

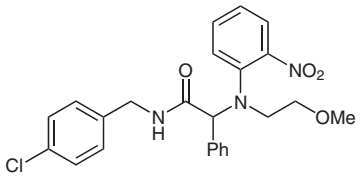
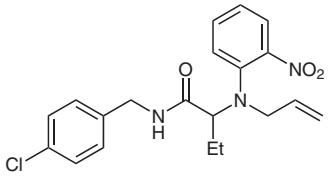
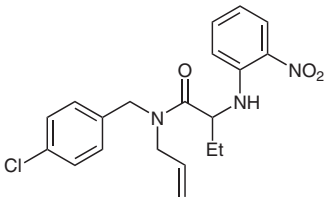
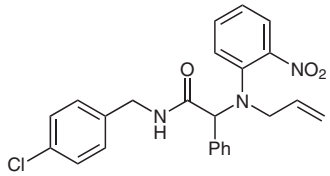
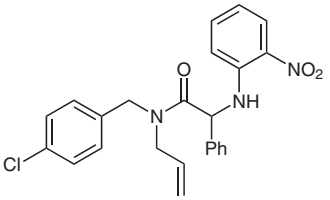
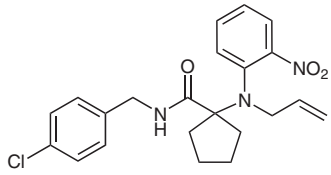
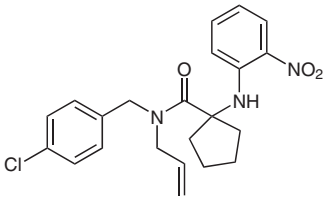
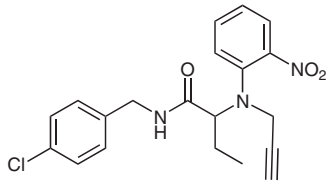
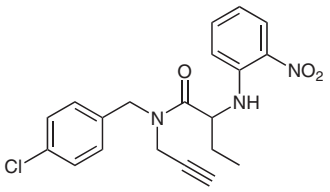
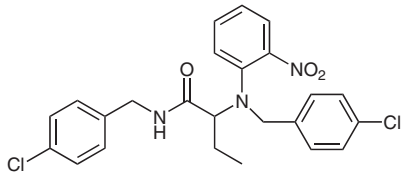
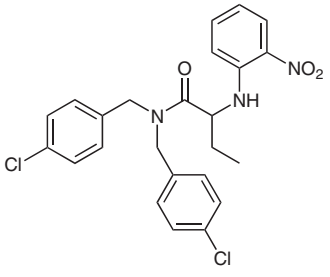
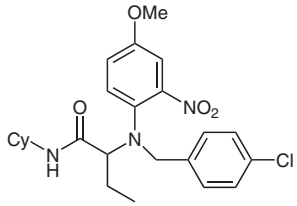
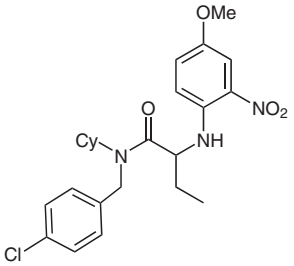
Surprisingly, no migration was observed when treating compound **1i** under the same conditions (Table 2, entry 1). In general, Ugi–Smiles adducts resulting from the condensation of a *p*-nitrophenol failed to rearrange in a similar way. Nevertheless, when substituted with a heteroatom



Scheme 1 Allyl shift in Ugi–Smiles adducts under basic conditions

SYNLETT 2011, No. 13, pp 1816–1820
Advanced online publication: 21.07.2011
DOI: 10.1055/s-0030-1260964; Art ID: D14211ST

Table 1 Scope of the Alkyl Shift with *o*-Nitro Derivatives

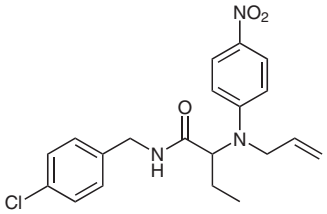
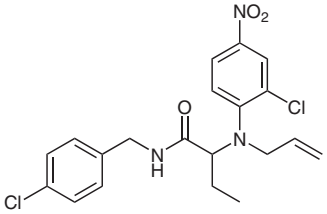
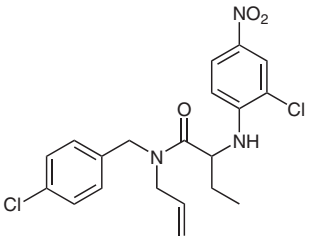
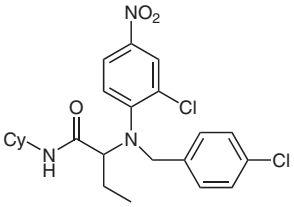
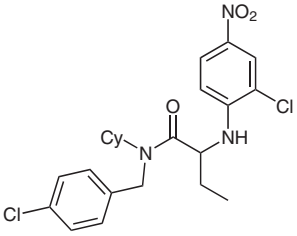
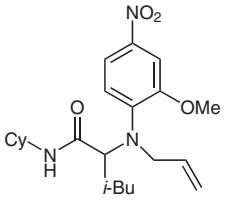
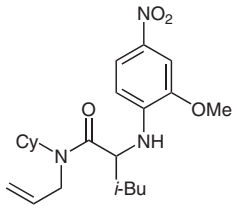
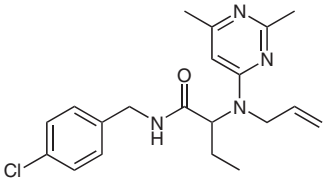
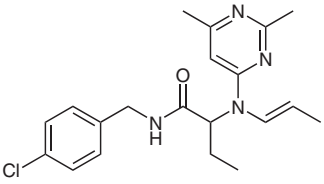
Entry	Starting material	Product	Yield (%)
1	 **1b**	–	–
2	 **1c**	 **2c**	81
3	 **1d**	 **2d**	77
4	 **1e**	 **2e**	86
5	 **1f**	 **2f**	88
6	 **1g**	 **2g**	64
7	 **1h**	 **2h**	71

at the *ortho* position, they behave as *o*-nitroaryl carboxamides do (Table 2, entries 2–4). We imagine that these *ortho* substituents may stabilize further the salt after migration through chelation of the metal cation. Finally, heteroaryl-substituted Ugi–Smiles adducts behave quite differently as no rearranged product could be isolated; only, on lengthening the reaction time with allyl derivatives, an isomerization of the double bond to give the more stable heteroaryl enamine was observed (Table 2, entry 5).

These rearrangements raise several questions concerning their mechanism. To assess the intra- or intermolecular nature of the process, an equimolar mixture of compound **1f** and **1l** was submitted to the NaH/MeCN conditions. No cross adduct could be detected, and the corresponding **2f** and **2l** were isolated in good yields. These results are consistent with an intramolecular rearrangement.

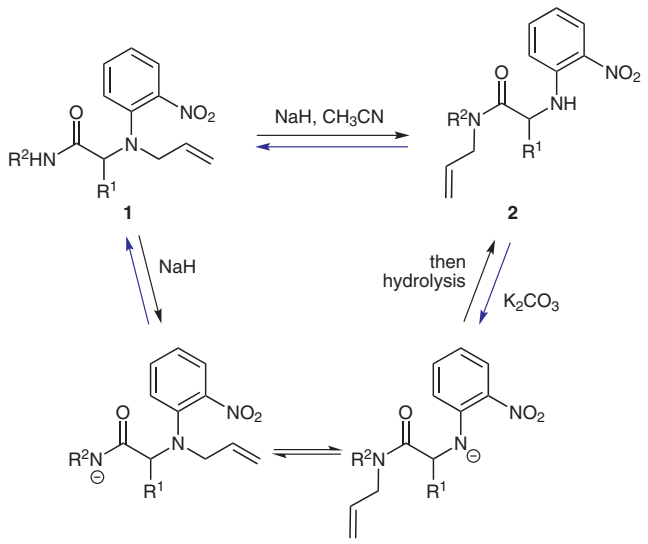
The reverse migration is more difficult to explain. This behavior was confirmed for benzylic derivatives as **2g**, left for few hours at room temperature in acetonitrile with potassium carbonate, reverts quantitatively to **1g**. The respective migratory properties of allyl and benzyl groups may be illustrated by the reaction of compound **2e** which may transfer either the allyl or the benzyl residue under treatment with potassium carbonate in acetonitrile. Although the configuration of the amide has to be examined more carefully in relation in this instance, the exclusive

Table 2 Influence of the Aryl Moiety on the Shift

Entry	Starting material	Product	Yield (%)
1	 **1i**	–	–
2	 **1j**	 **2j**	78
3	 **1k**	 **2k**	66
4	 **1l**	 **2l**	78
5	 **1m**	 **2m**	–

formation of allyl aniline **1e** is consistent with a lower migratory ability of the benzyl group.

The recovery of starting allyl or benzyl derivatives under treatment with potassium carbonate is certainly associated with an equilibrium between the aniline and amide anions. Under strongly basic conditions, the amide anion further evolves to give the more thermodynamically stable *N*-aryl anion which is quenched at the end of the reaction giving the NH-aryl adduct **2** (Scheme 3). However, in the presence of traces of a base, **2** gives the *N*-aryl anion in equilibrium with the more basic secondary amide anion which may be protonated by starting **2**. Once the amide is protonated, potassium carbonate is not basic enough to reform the amide causing a shift of the equilibrium towards **1**. This was confirmed when **2a** was treated by a catalytic amount of sodium hydride in acetonitrile, **1a** could be then quantitatively recovered after leaving the reaction overnight at room temperature.



Scheme 3 Base-promoted equilibria

In conclusion, we have disclosed a new rearrangement of Ugi-type adducts under basic conditions. The reaction is reversible and controlled by the amount of base used in the reaction medium. We are currently studying synthetic applications involving potential trapping of the aniline anion generated in the process.

General Procedure for the Synthesis of Migrated Products

To a 0.5 M solution of Ugi–Smiles adduct in MeCN was added NaH (95%, 1.5 equiv) at 0 °C. The resulting mixture was stirred at r.t. until completion, then quenched with a sat. aq solution of NH_4Cl, and extracted with EtOAc. The organic phases were collected and concentrated in vacuo to afford migrated products after purification by flash column chromatography on silica gel.

***N*-Allyl-*N*-(4-chlorobenzyl)-2-(2-nitrophenylamino) Butanamide (2c)**

Prepared from **1c** in a 0.5 mmol scale and isolated as 0.6:0.4 mixture of two rotamers (A/A^1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10–8.06 (m, 1 H), 7.58–7.48 (m, 2 H), 7.29–7.23 (m, 2 H), 7.15 (d, 1 H, *J* = 8.3 Hz), 7.12 (d, 1 H, *J* = 8.3 Hz), 6.90–6.85 (m, 1 H), 5.81–5.67 (m, 1 H), 5.75 (d, 0.4 H, *J* = 14.6 Hz, H-A^1), 5.66 (d, 0.6 H, *J* = 14.6 Hz, H-A), 5.11 (d, 0.6 H, *J* = 14.6 Hz), 5.07 (d, 0.4 H, *J* = 14.6 Hz), 4.98 (d, 1 H, *J* = 10.4 Hz), 4.11 (d, 0.6 H, *J* = 14.6 Hz), 4.02 (d, 0.4, *J* = 14.6 Hz), 3.20 (dd, 0.6 H, *J* = 5.8, 13.9 Hz), 3.12 (dd, 0.4 H, *J* = 5.8, 13.9 Hz), 2.98 (dd, 0.4 H, *J* = 5.8, 13.9 Hz), 2.92 (dd, 0.6 H, *J* = 5.8, 13.9 Hz), 2.83 (dd, 0.4 H, *J* = 5.3, 7.3 Hz), 2.75 (dd, 0.6 H, *J* = 4.3, 7.3 Hz), 1.79 (br s, 1 H), 1.56–1.47 (m, 0.8 H), 1.44–1.33 (m, 1.2 H), 0.80 (t, 1.2 H, *J* = 7.6 Hz), 0.78 (t, 1.8 H, *J* = 7.6 Hz). ^{13}C NMR of A (100.6 MHz, $CDCl_3$): δ = 174.4, 146.6, 136.7, 135.3, 134.4, 133.7, 132.5, 130.6, 129.8, 128.7, 126.0, 115.5, 59.8, 52.2, 49.9, 26.8, 10.3. ^{13}C NMR of A^1 (100.6 MHz, $CDCl_3$): δ = 174.3, 146.8, 136.7, 135.3, 134.4, 133.7, 132.5, 130.7, 129.7, 128.6, 125.9, 115.8, 59.4, 52.2, 50.2, 25.6, 10.1. IR (thin film): 2970, 2857, 1662, 1601, 1531, 1488, 1352, 1277, 1263, 1093, 1018 cm^{-1}. HRMS: *m/z* calcd for $C_{20}H_{22}ClN_3O_3$: 387.1350; found: 387.1354.

***N*-(4-Chlorobenzyl)-2-(2-nitrophenylamino)-*N*-(prop-2-ynyl) Butanamide (2f)**

Prepared from **1f** in a 1 mmol scale and isolated as 0.55:0.45 mixture of two rotamers (A/A^1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13–8.06 (m, 1 H), 7.58–7.52 (m, 2 H), 7.22 (d, 1 H, *J* = 4.5 Hz), 7.20 (d, 1 H, *J* = 4.5 Hz), 7.13 (d, 1 H, *J* = 8.3 Hz), 7.09 (d, 1 H, *J* = 8.3 Hz), 7.04–6.99 (m, 0.45 H), 6.92–6.87 (m, 0.55 H), 5.69 (d, 0.45 H, *J* = 14.6 Hz), 5.55 (d, 0.55 H, *J* = 14.6 Hz), 4.10 (d, 0.55 H, *J* = 14.6 Hz), 4.00 (d, 0.45 H, *J* = 14.6 Hz), 3.39 (dd, 0.45 H, *J* = 2.3, 16.4 Hz), 3.25 (t, 1 H, *J* = 3.0 Hz), 3.18 (dd, 0.55 H, *J* = 2.5, 16.4 Hz), 2.97 (dd, 0.45 H, *J* = 4.5, 7.6 Hz), 2.90 (dd, 0.55 H, *J* = 4.5, 7.6 Hz), 2.01 (t, 0.45 H, *J* = 2.5 Hz), 1.96 (br s, 1 H), 1.92 (t, 0.55 H, *J* = 2.5 Hz), 1.57–1.45 (m, 0.9 H), 1.45–1.30 (m, 1.1 H), 0.76 (t, 3 H, *J* = 7.6 Hz). ^{13}C NMR of A (100.6 MHz, $CDCl_3$): δ = 173.9, 146.2, 134.8, 134.3, 133.9, 133.8, 133.4, 130.5, 129.9, 128.7, 126.2, 81.7, 71.0, 59.1, 52.2, 36.5, 26.7, 10.1. ^{13}C NMR of A^1 (100.6 MHz, $CDCl_3$): δ = 173.8, 146.6, 135.0, 134.1, 133.9, 133.7, 132.5, 130.9, 129.7, 128.6, 126.0, 82.0, 71.6, 59.2, 52.4, 36.7, 25.7, 10.0. IR (thin film): 2928, 2857, 1662, 1606, 1531, 1493, 1394, 1347, 1272, 1089, 1013 cm^{-1}. HRMS: *m/z* calcd for $C_{20}H_{20}ClN_3O_3$: 385.1193; found: 385.1195.

Acknowledgment

S.R.P. thanks the ANR-CP2D Program (ANR MUSE) for a postdoctoral fellowship.

References and Notes

(1) (a) El Kaïm, L.; Grimaud, L.; Oble, J. *Angew. Chem. Int. Ed.* **2005**, *117*, 7961. (b) El Kaïm, L.; Gizolme, M.; Grimaud, L.; Oble, J. *J. Org. Chem.* **2007**, *72*, 4169. (c) Barthelon, A.; El Kaim, L.; Gizolme, M. *Eur. J. Org. Chem.* **2008**, 5974.

(2) (a) El Kaim, L.; Gizolme, M.; Grimaud, L.; Oble, J. *J. Org. Chem.* **2007**, *72*, 5835. (b) Oble, J.; El Kaim, L.; Gizzi, M.; Grimaud, L. *Heterocycles* **2007**, *73*, 503. (c) El Kaim, L.; Grimaud, L.; Gizzi, M. *Org. Lett.* **2008**, *10*, 3417. (d) Coffinier, D.; El Kaim, L.; Grimaud, L. *Org. Lett.* **2009**, *11*, 995. (e) Barthelon, A.; Legoff, X.-F.; El Kaim, L.; Grimaud, L. *Synlett* **2010**, 153. (f) El Kaïm, L.; Grimaud, L. *Mol. Diversity* **2010**, *14*, 855. (g) El Kaim, L.; Grimaud, L.; Wagschal, S. *J. Org. Chem.* **2010**, *75*, 5343. (h) El Kaim, L.; Grimaud, L.; Wagschal, S. *Chem. Commun.* **2011**, *47*, 1887.

(3) (a) El Kaim, L.; Gamez-Montaño, R.; Grimaud, L.; Ibarra-Rivera, T. *Chem. Commun.* **2008**, 1350. (b) El Kaim, L.; Grimaud, L.; Legoff, X.-F.; Schiltz, A. *Org. Lett.* **2011**, *13*, 534.

(4) (a) El Kaim, L.; Grimaud, L.; Wagschal, S. *J. Org. Chem.* **2010**, *75*, 5343. For similar synthetic strategies with classical Ugi adducts, see: (b) Marcaccini, S.; Pepino, R.; Pozo, M. C. *Tetrahedron Lett.* **2001**, *42*, 2727. (c) Bossio, R.; Marcos, C. F.; Marcaccini, S.; Pepino, R. *Heterocycles* **1997**, *45*, 1589. (d) Bossio, R.; Marcos, C. F.; Marcaccini, S.; Pepino, R. *Synthesis* **1997**, 1389.

(5) This term has been mainly used for the 'halogen-dance reaction'. It involves migration of halogen atoms when aryl derivatives are treated under basic conditions. See: Bunnett, J. F. *Acc. Chem. Res.* **1972**, *5*, 139. For a more recent use, see: Stanetty, P.; Schnürch, M.; Mereiter, K.; Mihovilovic, M. D. *J. Org. Chem.* **2005**, *70*, 567.