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Multicomponent Reactions

Predicting New Ugi–Smiles Couplings: A Combined Experimental and Theoretical Study

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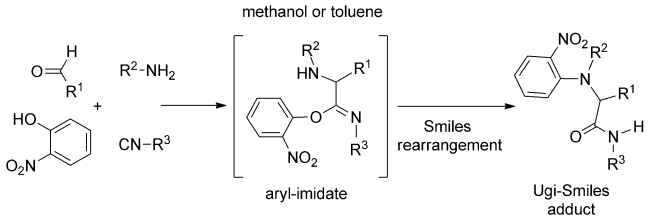
Abstract: Following our previous mechanistic studies of multicomponent Ugi-type reactions, theoretical calculations have been performed to predict the efficiency of new substrates in Ugi–Smiles couplings. First, as predicted, 2,4,6-trichlorophenol experimentally gave the corresponding aryl-imidate. Theoretical predictions of nitrosophenols as good acidic partners were then successfully confirmed by experiments. In the latter case, the reaction offers a new access to benzimidazoles.

Introduction

The Ugi reaction[1,2] is one of the most famous and efficient multicomponent reactions. Its popularity, first due to the versatility of the products easily transformed into heterocycles, was dramatically impacted throughout the last decades by new trends in chemistry. Indeed, recent growing environmental concerns in organic chemistry shed some light on multicomponent couplings as they fit both concepts of step and atom economy in chemistry. A few years ago, we reported a variant, coined as the Ugi–Smiles reaction, by replacing the carboxylic acid with an electron-deficient phenol (Scheme 1).[3] The reaction could be performed on 2- and 4-nitrophenols, salicylic esters as well as various heterocycles, such as hydroxypyridines or pyrimidines.[4]



Scheme 1. Ugi–Smiles couplings.

The synthetic potential of this reaction together with some surprising results observed with substituted phenols led us to perform theoretical calculations to obtain a better insight into the mechanism of the reaction. The whole mechanistic path was first studied with 2-nitrophenol considering acetaldehyde, methylamine and methylisocyanide as the three other partners.[5] This study pointed out two rate-determining steps. The first activation barrier concerns the nucleophilic addition of the isocyanide on the activated imine to give the corresponding nitrilium, and equals 17.6 kcal mol^{-1} in toluene (Scheme 2, **2**→**TS-1**→**3**). The final Smiles rearrangement constitutes the second rate-determining step of the process and can be considered as a concerted process due to the shallow nature of the spiro intermediate. Its activation energy was calculated to be 20.6 kcal mol^{-1} (Scheme 2, **4**→**TS-4**→**6**). These two barriers were evaluated and compared for a wide variety of phenols.[6]

These theoretical studies led us to rationalize most of the results previously observed during the experimental screening of the reaction. The good correlation between yields and computed activation energies led us to envision using these energies as predictive tools to discover new partners for this coupling. Herein, we present the results of this approach applied to halogenated and nitroso phenols.

Results and Discussion

As halogenated phenols are well-known substrates in aromatic nucleophilic substitutions,[7] calculations of the two activation

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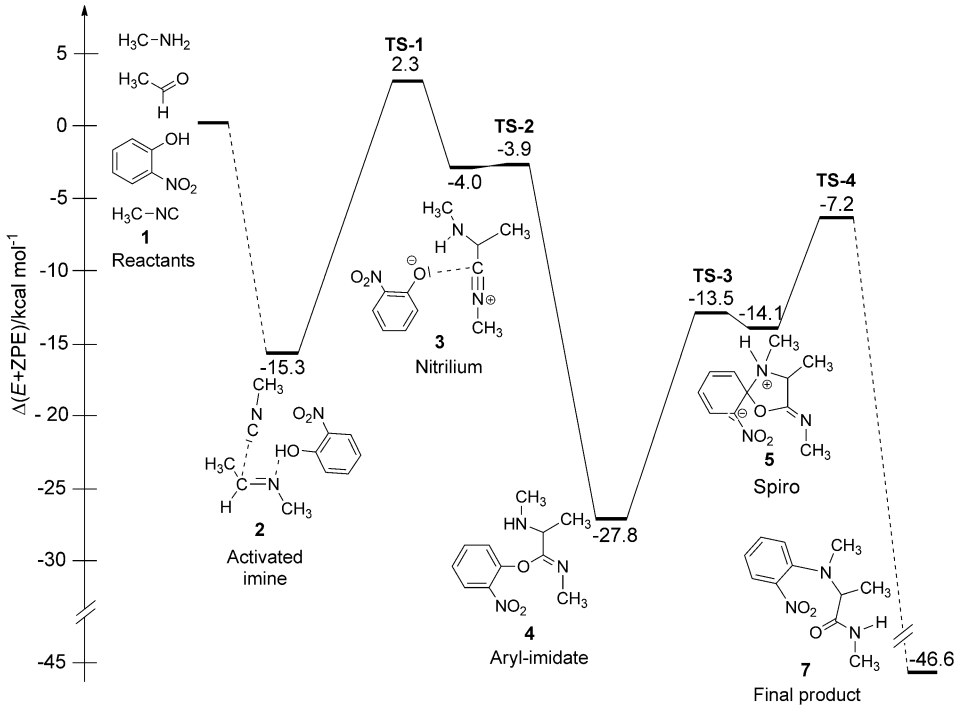
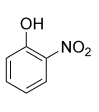
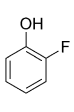
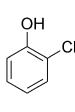
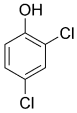
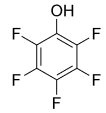
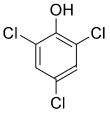


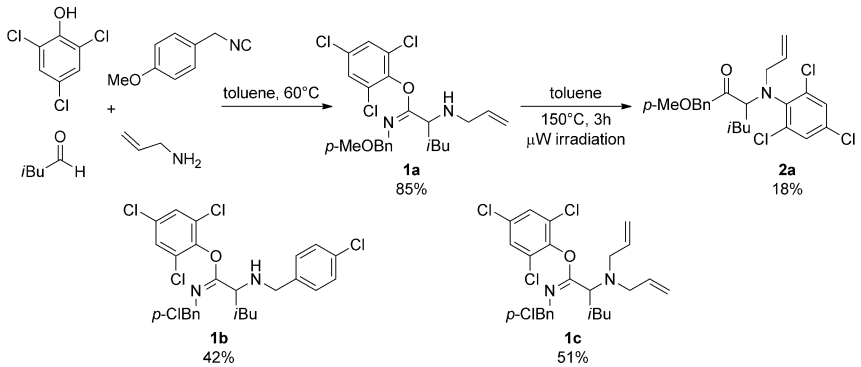
Scheme 2. Energy profile of the mechanism of a model Ugi–Smiles reaction. Calculations were carried out at the M06-2X/6-311 + G(d,p) level of theory in toluene.

energies for the Ugi–Smiles process were performed with a variety of fluorinated and chlorinated phenols (Table 1). Energies were calculated with Gaussian 09[8] using density functional theory at the M06-2X/6-311 + G(d,p) level[9] and corrected with zero point energy (ZPE). Transition states were localized by using the string method as implemented in the Opt'n Path software.[10] Solvent effects were modeled by a polarizable continuum model (PCM) as implemented in Gaussian 09[11] and results are quite similar in both methanol and toluene (see the Supporting Information for the results obtained in methanol). When considering the results for 2-fluorophenol, the high activation energy observed for the first step (27.4 kcal mol^{-1}) should prevent the success of the four-component coupling. Similarly, 2-chloro- and 2,4-dichlorophenols should not promote the desired reaction with, respectively, 24.2 and 23.0 kcal mol^{-1} of activation barriers. However, pentafluorophenol and 2,4,6-trichlorophenol provided relatively low energies for the first step: 19.5 and 21.2 kcal mol^{-1}, respectively. These values are comparable to the one obtained with methyl *ortho*-hydroxybenzoate in methanol (20.1 kcal mol^{-1}), which is an efficient partner.[6] This led us to test these two new phenols in Ugi–Smiles couplings, even if the Smiles barrier seemed to be difficult to overcome. Pentafluorophenol was first tested in standard Ugi–Smiles conditions (4 h at 60 °C in toluene) but no coupling with the three other partners could be observed, probably due to the instability of the aryl-imidate. Gratifyingly, when 2,4,6-trichlorophenol was treated in the same conditions with isovaleraldehyde, allylamine and *para*-methoxybenzylisocyanide, the product **1a** was isolated in 85% yields (Scheme 3). Compound **1a** is the aryl-imidate intermediate (Scheme 2), which did not undergo the Smiles rearrangement. This observation is consistent with the high energy barrier found for this final step. Thus, the aryl-imidate **1a** is considered to be trapped in an energy well, as predicted by the calculations. A similar reaction occurred with other partners affording compounds **1b–c**, still without Smiles rearranged product (Scheme 3). Prolonged

Table 1. Activation barriers of the two rate-determining steps for halogenated phenols in toluene.

Phenol						
$\Delta E^{\#}$ (nitrilium)[a]	17.6	27.4	24.2	23.0	19.5	21.2
$\Delta E^{\#}$ (Smiles)[a]	20.6	32.5	31.2	31.7	31.6	30.5

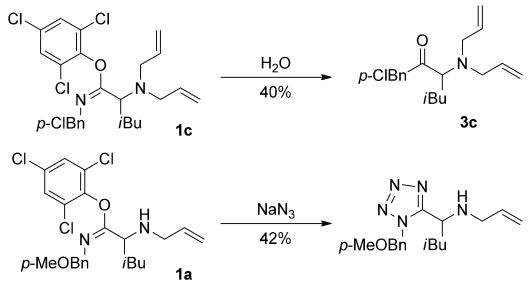
[a] All energies are given in kcal mol^{-1}.



Scheme 3. 2,4,6-Trichlorophenol promotes aryl imidate formation.

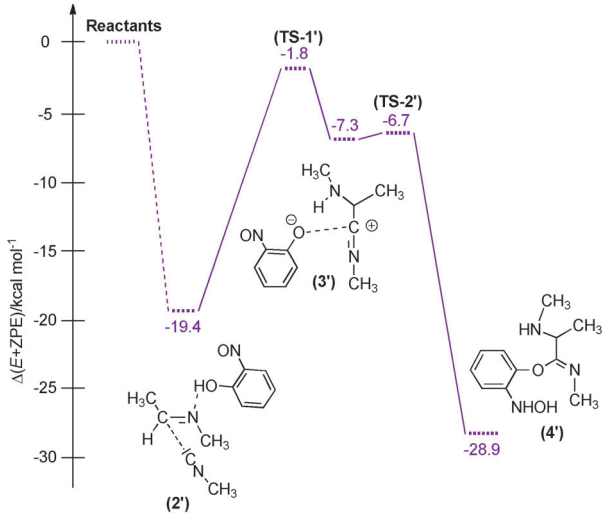
heating of **1a** at 150 °C under microwave irradiation provided the corresponding *N*-aryl carboxamide **2a** in low yield (around 15% estimated by ^{1}H NMR analysis) probably due to partial decomposition at this temperature.

At this stage, we surmised that 2,4,6-trichloroarylimidates **1a**–**c** could be considered as masked nitrilium reluctant to perform Ugi-type reactions. To test this hypothesis, hydrolysis of the aryl imidate **1c** was performed yielding 40% of the corresponding carboxamide **3c**. Different nucleophiles (acetic acid, potassium carboxylate, tetrazoles, etc.) were then tested with **1**; except for water or sodium azide, no evolution of the imidate was observed (Scheme 4). Nevertheless, the use of 2,4,6-trichlorophenol constituted the first success in the prediction of the efficiency of a four-component coupling by theoretical calculations.



Scheme 4. Nucleophilic additions on 2,4,6-trichloroaryl imidates.

To further develop the potential of this predictive tool, non-commercially available substituted phenols were next examined. 2-Nitrosophenol was selected due to the ability of the nitroso group to be involved in addition or cycloaddition reactions, which could further open the field to various postcondensation transformations of the Ugi–Smiles adducts. As previously, theoretical calculations were performed by using acetaldehyde, methylamine and methylisocyanide as model reactants (Scheme 5). The first activation energy with 2-nitrosophenol was found to be the same as the one obtained with 2-nitrophenol, which should ensure the aryl-imidate formation.



Scheme 5. Formation of the aryl-imidate with 2-nitrosophenol in toluene.

Interestingly, some differences emerged when studying the Smiles rearrangement of the aryl imidate (**4′**). As already observed, the formation of the Meisenheimer complex is facilitated by "built-in-solvation" with a heteroatom at the *ortho* position of the hydroxyl group (Scheme 6).[12] However, in the case of 2-nitrosophenol, this interaction is so strong that a proton transfer occurs during the nitrogen addition to the aryl. This transfer considerably stabilizes the spiro intermediate (**5′a**), which turns out to be more stable than the aryl-imidate (**4′**). It is worth noting that such a proton transfer is unlikely with 2-nitrophenol derivatives: the protonated 2-nitro-derivative analogue to **5′a** is located 2.1 kcal mol^{-1} above the spiro compound. The cyclization leading to **5′a** is associated with an activation energy lower than with the 2-nitrophenol: 12.7 versus 14.3 kcal mol^{-1}. Once **5′a** is formed, breaking the new C–N bond costs more energy than in the case of the nitro group, as the leaving group is no longer a neutral amine but a negatively charged one with reduced nucleofugacity. In this case, the spiro ring opening (Scheme 6, **5′a**→**TS-4′a**→**7′**) constitutes the second rate-determining step of the Ugi–Smiles reaction with a barrier of 22.9 kcal mol^{-1}.

Alternative mechanistic paths were also considered to avoid this hydrogen transfer by modifying the relative orientation of the nitroso and of the amino groups (see the Supporting Information). In this case, the spiro-cyclization requires 14.8 kcal mol^{-1} to proceed, resulting in the spiro **5′b**, which can easily evolve with only 6.5 kcal mol^{-1} of barrier (Scheme 7). Kinetic calculations (detailed in the Supporting Information) of the different paths pointed out that this alternative path is kinetically favored over the first one even if the most energetic structure is slightly higher in energy (20.0 vs. 19.0 kcal mol^{-1}). As a consequence, the Smiles rearrangement of the 2-nitrosophenol can be considered as a one-step process with an overall barrier equal to 20.0 kcal mol^{-1}.

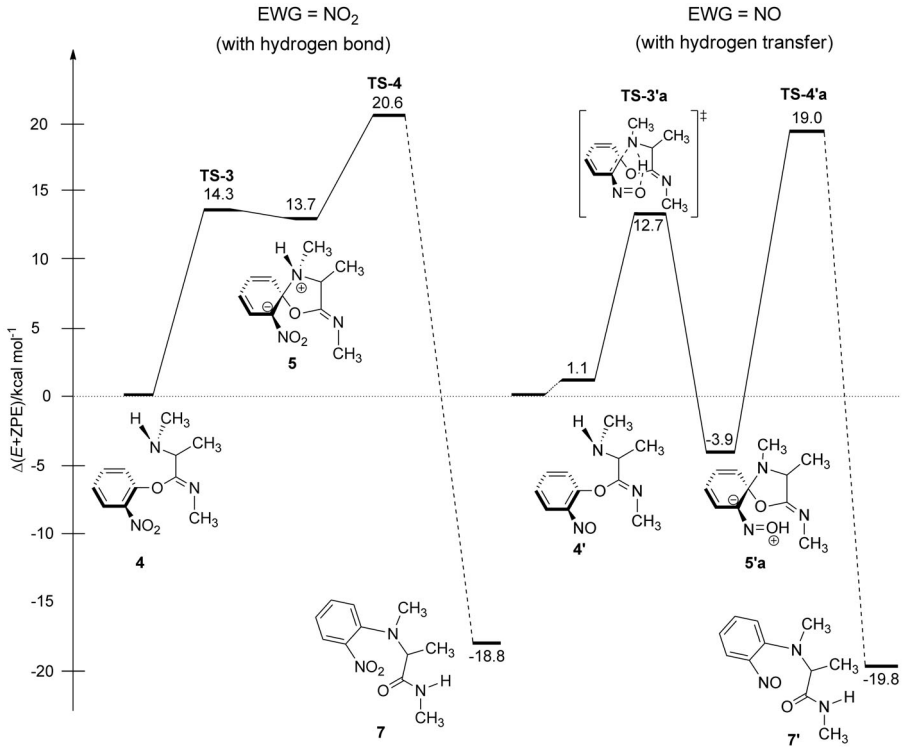
Regarding the computed activation energies for the two rate-determining steps, 2-nitrosophenols should be good partners in Ugi–Smiles couplings (Table 2). Therefore, various 2-nitrosophenols were prepared through nitrosation of 4-substituted phenols under treatment with sodium nitrite and nitric acid (Scheme 8).

Table 2. Activation energies [kcal mol^{-1}] for 2-nitro and 2-nitroso phenols in toluene.

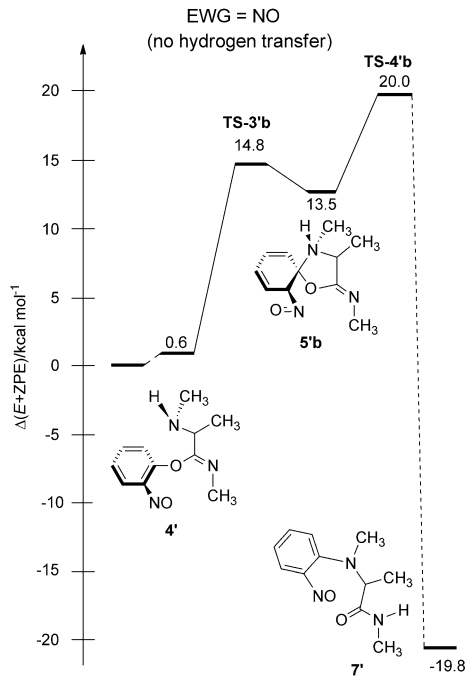
Phenol		
$\Delta E^{\#}$ (aryl imidate)	17.6	17.6
$\Delta E^{\#}$ (Smiles)[a]	20.6	20.0

[a] Energies for the Smiles rearrangement are given for the most favored pathway.

To our delight, the desired Ugi–Smiles product **4a** was isolated in 72% yield after prolonged stirring of a stoichiometric



Scheme 6. Smiles rearrangement with hydrogen interaction at the *ortho* position.

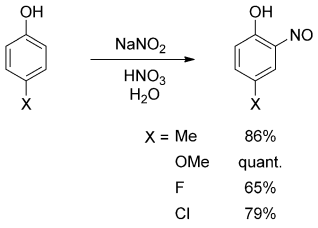


Scheme 7. Favored Smiles rearrangement without H interaction with the NO group.

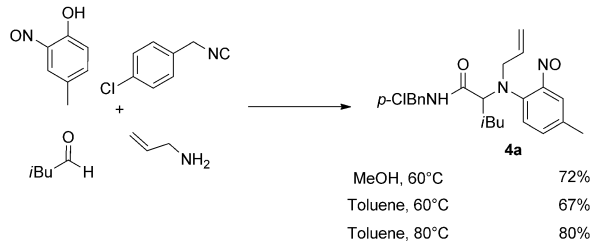
mixture of 4-methyl-2-nitrosophenol, isovaleraldehyde, allylamine and *para*-chlorobenzylisocyanide in methanol at 60 °C. This result can be slightly improved to 80% in toluene at 80 °C (Scheme 9). These experimental results further validated our theoretical predictions.

The scope of the reaction was then investigated as displayed in Table 3. Various nitroso phenols were tested with a large set of aliphatic or aromatic aldehydes and ketones. The coupling was efficient with both electron-donating (Table 3, entries 1–11) and -withdrawing substituents (Table 3, entries 12 and 13) on the aromatic core. Allyl and benzylamines are very efficient but simple primary alkylamines react as well (Table 3, entry 6). No limitation was observed concerning the isocyanide: both alkyl, even the hindered *tert*-butyl derivative, and benzyl isocyanides gave good yields.

As already reported for different families of Ugi–Smiles adducts,[1g,4b,c] the nitroso moiety afforded various possibilities for



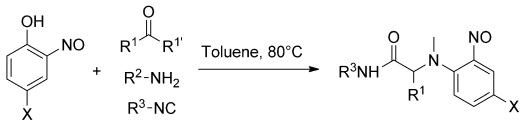
Scheme 8. 2-Nitrosophenol synthesis.



Scheme 9. First Ugi–Smiles coupling with 4-methyl-2-nitrosophenol.

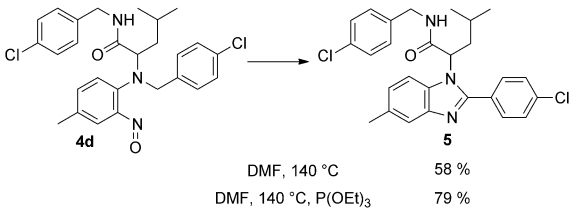
postcondensation transformations. Indeed, nitroso groups are known to react in additions or cycloadditions. To demonstrate the potential of such a functional group, **4d** was heated in DMF at 140 °C. Under these conditions, the corresponding benzimidazole was isolated in 58% yield (Scheme 10). The formation of this heterocycle can be optimized to 79% using triethylphosphite as proposed for the reduction of nitro by Cado-

Table 3. Scope of the Ugi–Smiles coupling with 2-nitroso phenols.



Entry	X	$R^1COR^{1'}$	R^2NH_2	R^3NC	Product (yield [%])
1	Me	*i*BuCHO	*p*-MeOBnNH$_2$	*p*-ClBnNC	**4b** (80)
2	Me	$C_6H_{13}CHO$	AllNH$_2$	*p*-ClBnNC	**4c** (56)
3	Me	*i*BuCHO	*p*-ClBnNH$_2$	*p*-ClBnNC	**4d** (79)
4	Me	*i*BuCHO	*m*-MeOBnNH$_2$	*p*-ClBnNC	**4e** (88)
5	Me	*i*BuCHO	AllNH$_2$	CyNC	**4f** (90)
6	Me	*i*BuCHO	*c*-$C_3H_5NH_2$	*p*-ClBnNC	**4g** (58)
7	Me	*i*BuCHO	*p*-FBnNH$_2$	*p*-ClBnNC	**4h**(88)
8	Me	*i*BuCHO	*p*-ClBnNH$_2$	Ar(CH$_2$)$_2$NC[a]	**4i** (90)
9	Me		AllNH$_2$	*p*-ClBnNC	**4j** (58)
10	Me	*i*BuCHO	*o*-ClBnNH$_2$	*p*-ClBnNC	**4k** (62)
11	OMe	*i*BuCHO	*p*-MeOBnNH$_2$	*p*-ClBnNC	**4l** (72)
12	F	*i*BuCHO	*p*-MeOBnNH$_2$	*p*-ClBnNC	**4m** (65)
13	Cl	ArCHO[a]	AllNH$_2$	*t*BuNC	**4n** (74)[b]

[a] Ar = 3,4-(MeO)$_2$C$_6$H$_3$. [b] The reaction was performed in degassed methanol as solvent.



Scheme 10. Benzimidazole synthesis from Ugi–Smiles adduct **4d**.

gan, according to a procedure similar to the one reported for nitro adducts.[13,14]

Conclusions

In the present study, theoretical calculations have been used to propose new potential partners in the 4-component Ugi–Smiles coupling. Halogenophenols were first considered: as predicted, 2,4,6-trichlorophenol led to the corresponding arylimidates, the Smiles rearrangement being associated with a too high energy barrier to proceed. Nitrosophenols were then successfully tested after proving by DFT calculations that they should be good candidates for the Ugi–Smiles coupling. This study brings a further demonstration of the value of merging experimental and theoretical methods to progress the study of new reactions.[15] The Ugi–Smiles coupling was initially discovered trying to combine Smiles rearrangements with Ugi couplings. The choice of the phenols was then mainly dictated by their previous use in Smiles rearrangements. These first experimental observations gave us enough data to benchmark the accuracy of the computational method, which in turn led to the proposition of new substrates for the coupling. Although, to the best of our knowledge, there was no precedent of Smiles rearrangement involving a nitroso group, the straightforward calculation of the energy barriers for the nitroso group was a strong incentive to work on the preparation of several nitrosophenols.

Experimental Section

Typical procedure for trichlorophenol addition given for 1a

Allylamine (75 μL, 1.0 mmol), *para*-methoxybenzylisocyanide (150 μL, 1.0 mmol) and 2,4,6-trichlorophenol (181 mg, 1.0 mmol) were added to a solution of isovaleraldehyde (107 μL, 1.0 mmol) in toluene (1 mL). The mixture was stirred at 80 °C for 4 h under an argon atmosphere. The volatile materials were then removed under reduced pressure to afford the crude product. The latter was purified by flash column chromatography on silica gel (petroleum ether/diethyl ether 90:10 to 80:20) to obtain the desired product as a yellow-orange oil (80%, 331 mg).

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.25$ (s, 2H), 7.00 (d, $J = 8.6$ Hz, 2H), 6.75 (d, $J = 8.6$ Hz, 2H), 5.90–5.83 (m, 1H), 5.06 (dd, $J = 17.2$, 1.4 Hz, 1H), 5.01 (dd, $J = 10.2$, 1.4 Hz, 1H), 5.43–4.33 (m, 2H), 3.76 (m, 1H), 3.67 (s, 3H), 3.42 (dd, $J = 13.7$, 5.4 Hz, 1H), 3.15 (dd, $J = 13.7$, 6.5 Hz, 1H), 1.85–1.75 (m, 1H), 1.69–1.52 (m, 2H), 0.86 (d, $J = 6.5$ Hz, 3H), 0.84 ppm (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 161.0$, 158.0, 144.9, 136.5, 132.0, 131.9, 130.5, 129.9, 128.5, 127.8, 116.4, 113.5, 55.1, 52.6, 50.5, 50.4, 42.5, 24.7, 22.9, 22.4 ppm; IR: $\tilde{\nu}_{bar} =$ 2955, 2871, 2833, 1688, 1613, 1583, 1512, 1444, 1387, 1275, 1258, 1248, 1177, 1127, 1035 cm^{-1}; HRMS: calcd for $C_{23}H_{27}Cl_3N_2O_2$: 468.1138, found: 468.1136.

Typical procedure for 2-nitrosophenol addition given for 4a

Allylamine (75 μL, 1.0 mmol), *p*-chlorobenzylisocyanide (150 μL, 1.0 mmol) and 4-methyl-2-nitrosophenol (137 mg, 1.0 mmol) were successively added to a solution of isovaleraldehyde (107 μL, 1.0 mmol) in toluene (1 mL) under argon. The reaction mixture was stirred for 18 h at 80 °C. The solvent was then removed under re-

duced pressure to afford the crude Ugi–Smiles product. The latter was purified by flash column chromatography on silica gel (petroleum ether/diethyl ether 85:15) to obtain the desired product as an orange-brown oil (80%, 331 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.37 (m, 2H), 7.22 (d, J = 8.3 Hz, 2H), 7.16–7.09 (m, 3H), 5.59–5.53 (m, 1H), 5.07(d, J=10.3 Hz, 1H), 5.06 (d, J = 17.2 Hz, 1H), 4.39 (d, J = 6.1 Hz, 2H), 3.77 (dd, J = 8.8, 5.3 Hz, 1H), 3.72 (dd, J = 15.3, 6.7 Hz, 1H), 3.41 (dd, J = 15.3, 5.6 Hz, 1H), 2.35 (s, 3H), 1.83 (ddd, J = 13.5, 8.8, 5.0 Hz, 1H), 1.67–1.56 (m, 1H), 1.40 (ddd, J = 13.5, 8.4, 5.3 Hz, 1H), 0.83 (d, J = 6.6 Hz, 3H), 0.80 ppm (d, J = 6.6 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.2, 146.0, 139.6, 136.9, 134.4, 133.5, 132.8, 129.1, 128.6, 125.2, 124.9, 118.8, 65.4, 52.9, 42.7, 38.6, 25.5, 23.1, 22.0, 20.5 ppm; IR: $\tilde{\nu}_{bar}$ = 3390, 2959, 2923, 2878, 1660, 1527, 1493, 1357, 1280, 1224, 1172, 1095, 1018 cm^{-1}; HRMS: calcd for $C_{23}H_{28}ClN_3O_2$: 413.1870, found: 413.1878.

Other products and characterizations are detailed in Supporting Information.

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Keywords: density functional calculations · multicomponent reactions · nitrosophenols · prediction · Ugi–Smiles coupling

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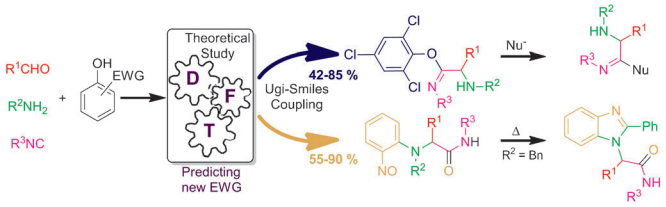

Cracking a Ugi–Smiles: Theoretical calculations were performed to predict the efficiency of new partners in Ugi–Smiles couplings. First, as predicted, 2,4,6-trichlorophenol experimentally gave the corresponding aryl-imidate (see scheme). Theoretical predictions of nitrosophenols as good acidic substrates were then successfully confirmed by experiments. In the latter case, the reaction offers a new access to benzimidazoles.

Multicomponent Reactions

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Predicting New Ugi–Smiles Couplings: A Combined Experimental and Theoretical Study