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Substituent Effects in Ugi-Smiles Reactions

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TITLE RUNNING HEAD: Substituent Effects in Ugi-Smiles Reactions

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ABSTRACT: In a recent communication, we described the mechanism of the well-known Ugi-type reactions with a model system (*J. Org. Chem.*, **2012**, *77*, 1361-1366). Herein, focusing on the Ugi-Smiles coupling, we study the effects of each of the four reactants on the energy profile to further explain the experimental results. The variations observed with different carbonyl compounds rely on their influence on the formation of the aryl-imidate, whereas the variations on the amine preferentially affect the Smiles rearrangement. The effect of substituents on the phenol derivative is seen on both aryl-imidate formation and the rearrangement. The effect of the isocyanide substituents is less pronounced.

KEYWORDS: Ugi reaction; isocyanide; density functional calculations; substituent effects.

1. Introduction

In the current context, synthetic chemists are looking for reactions leading to few side products under environmentally friendly conditions. Multicomponent reactions (MCR) have thus gained interest in the last two decades as they combine three or more reactants in a single adduct. In 1959, Ugi described the condensation of an amine, an aldehyde, an isocyanide and a carboxylic acid in a one-pot procedure.^{1,2} This reaction was one of the first to be used in the late 1980's for the creation of chemical libraries and is still widely studied nowadays due to the synthetic relevance of the *bis*-amide product.^{3,4} Shortly after his first report, Ugi extended this coupling to other acidic partners. This strategy, followed by other groups, led to the use of various acids such as H₂O, H₂S, RCOSH or HN₃...⁵⁻¹⁰ In 2005, El Kaïm and Grimaud proposed electron-poor phenols as acid surrogates in this coupling (see Figure 1).¹¹ In this case, the last step of the Ugi procedure is a Smiles rearrangement. A high number of variations of the reactants were carried out experimentally, and some results remain not fully understood.¹²

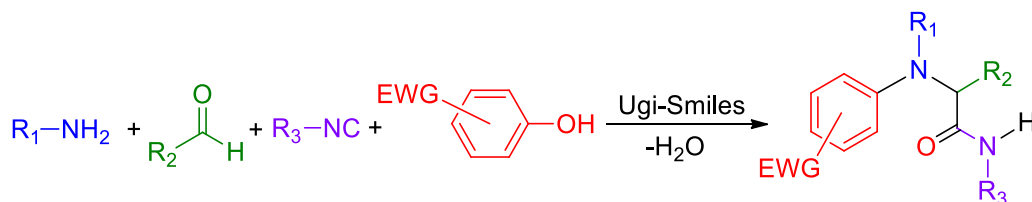


Figure 1. The Ugi-Smiles reaction (EWG=Electron-Withdrawing Groups).

To explain these experimental results and to build a predictive model, we started by studying the mechanism of the Ugi-Smiles reaction.¹³ Insight from DFT calculations revealed that the Ugi-Smiles and Ugi mechanisms are barely different (besides the final rearrangement). A simplified energy profile for a model Ugi-Smiles reaction is presented in Figure 2. A more detailed profile can be found in the Supporting Information. For the original Ugi reaction, Ugi suggested that all steps but the latter are equilibrated and that the final rearrangement shifts the equilibrium. However, the aryl-imidate (**4**) formation and the final rearrangement (**4**→**6**) appeared to be both rate determining steps and the driving forces of the reaction. A first set of experimental results was explained by the analysis of the Smiles rearrangement (**4**→**6**): to allow the reaction to proceed, an intramolecular hydrogen bond between the

ammonium and the substituent located on *ortho* of the hydroxyl in the starting phenol –NO₂ in Figure 2– is mandatory to balance the possible steric clashes (see (TS-4) scheme).¹⁴ When the starting phenol is substituted at the *ortho* position with a group which does not enable hydrogen bonds (methyl or allyl for example), the reaction does not proceed.

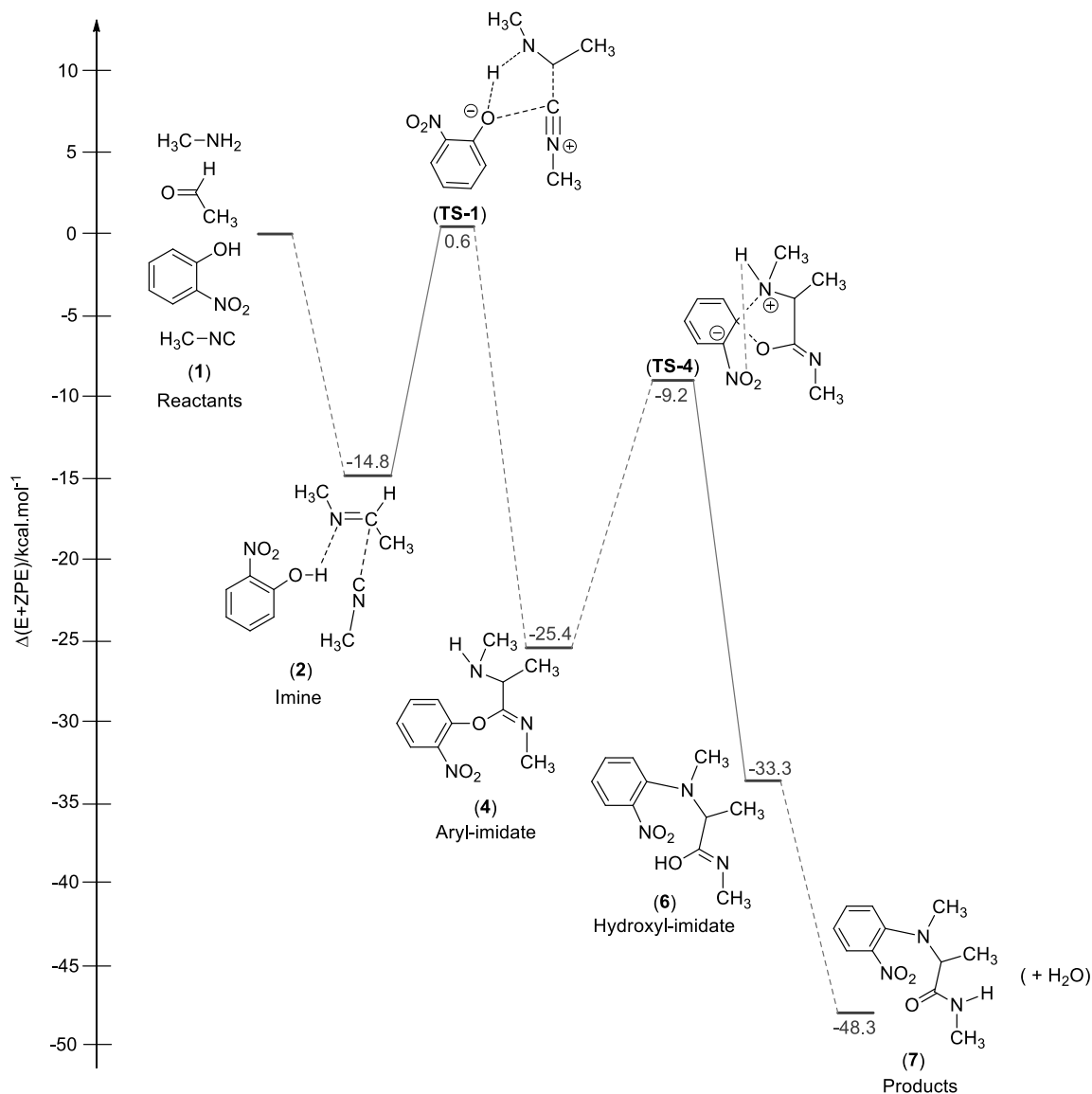


Figure 2. Simplified energy profile of the mechanism of a model Ugi-Smiles reaction. Calculations were done at the M06-2X/6-311+G(d,p) level of theory in methanol.

In the present article, we want to further understand and explain the experimental results. For example: (i) nitrothiophenol gives very low yields of the desired adducts with respect to the use of their nitrophenol analogues.^{12,15} This is surprising because thiophenols are more acidic than phenols, and

thiophenolates are more nucleophilic than the corresponding phenolates (see Figure 3); (ii) with some compounds such as methyl thiosalicylate¹⁵ the isolated product is the aryl-imidate (4) and not the final product (7) (see Figure 4) (whereas with methyl salicylate the yield is close to 80%); (iii) with anilines, no reaction proceeds even if the intermediate imine is preformed¹² (see Figure 5).

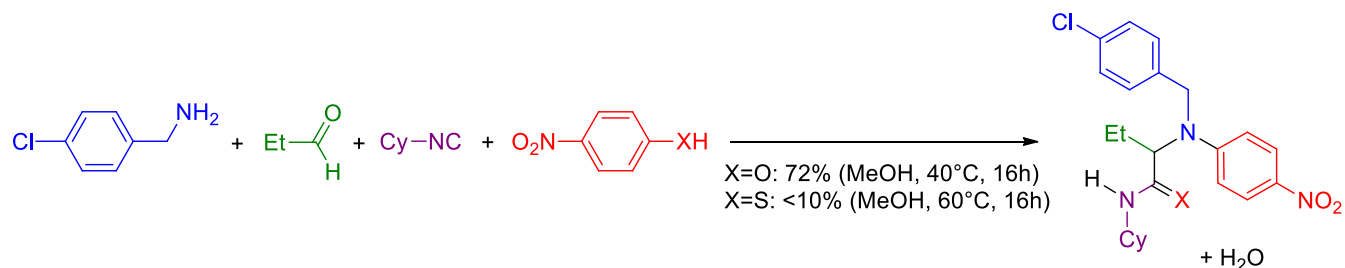


Figure 3. Comparison between 4-nitrophenol and 4-nitrothiophenol in the Ugi-Smiles coupling.

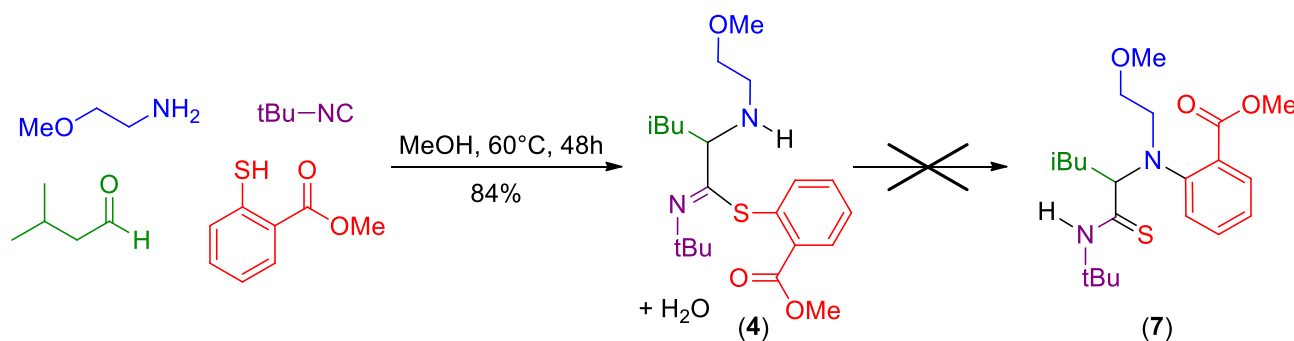


Figure 4. Use of methyl thiosalicylate in the Ugi-Smiles coupling.

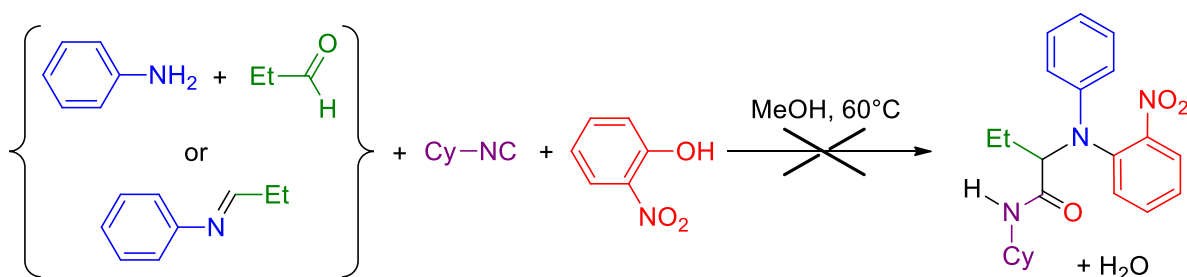


Figure 5. Use of the aniline in the Ugi-Smiles reaction.

To explain these results, the influence on the energy profile of each substituent was independently studied, considering mainly those experimentally used. New phenols –not tested yet– were investigated aiming at predicting new activating groups for this reaction.

2. Computational details

For the model system displayed in Figure 2, methylamine, acetaldehyde, methylisocyanide and *ortho*-nitrophenol were selected as partners in the coupling (for all reactants but the acid, we used a methyl group to describe the substituent). Unless otherwise mentioned, we computed the substituent influence of each reactant independently while the other three reactants remained those of the model system. In the following tables, the indicated yields are the best obtained with this starting material: if the best yield for a specific reactant is close to 100%, the activation energies should be consistent with the efficiency of the reaction; if the best yield is low (close to 10% e.g.) whereas the other partners lead to high yields otherwise, this reactant could be considered as responsible for this effect. The best obtained yield thus provides a measure of the influence of a reactant on the energy profile. The other reactants actually used to obtain the best yield are given in the SI for each variation.

We focused on the activation energies of the aryl-imidate formation ($2 \rightarrow \text{TS-1} \rightarrow 4$) and of the Smiles rearrangement ($4 \rightarrow \text{TS-4} \rightarrow 6$), as shown in Figure 1. For the latter step, we have shown that a concerted mechanism starting from the aryl-imidate (**4**) with a sole transition state energy of (**TS-4**) and a step-wise mechanism as displayed in Supporting Information ($4 \rightarrow \text{TS-3} \rightarrow 5 \rightarrow \text{TS-4} \rightarrow 6$) resulted in the same kinetic rate. Moreover, with some phenols (for example those without strong electron-withdrawing groups), a concerted mechanism is observed with a unique transition state similar in structure to (**TS-4**). Therefore, the energy of (**TS-3**) has no influence on the product formation, and we focused only on the (**TS-4**) energy. When possible, the privileged conformation involved a hydrogen bond in the spiro (**5**) (see Supporting Information). Several representative orientations were computed for every stationary point, and the most stable one was always selected. All the activation energies are computed with respect to the most stable pre-reactant complex.

Quantum mechanics calculations were performed with the Gaussian09 software package.¹⁶ Energies and forces were computed by density functional theory with the M06-2X¹⁷⁻¹⁹ exchange-correlation functional with a triple- ζ quality 6-311+G(d,p) basis set, and are corrected with the zero-point energy. Gibbs energies for all the variations are reported in Supporting Information. Overall, the trends and the

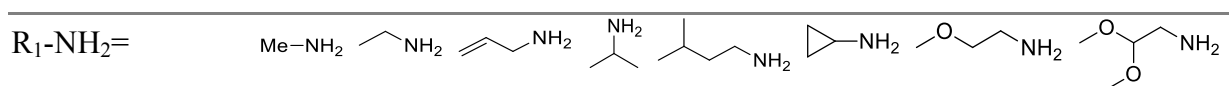
relative variations are the same and only the zero-point corrected energies are discussed here. A polarizable continuum model²⁰⁻²² (PCM) of solvent was used as implemented in Gaussian09 to describe the medium (methanol). Transition states were localized using the string theory²³ as implemented in Opt'nPath.²⁴ In the string theory,²³ as in the Nudged Elastic Band (NEB) approach,²⁵ the reaction path is described as an ensemble of intermediate structures (called images) that gradually change from the reactant geometry to the product geometry. Starting for an initial path (usually a linear interpolation), each intermediate structure is optimized. To prevent the images to collapse to the reactant or the product geometry, they are artificially linked by a (virtual) string. In the NEB approach, they are linked with artificial springs, which introduce the need to tune the artificial spring constants. In our implementation of the string method, each image evolves on the potential energy surface for a given number of steps. Then, they are re-distributed evenly on the string to ensure a homogeneous description of the whole reaction path. This theory is more robust than the QST methods and as efficient as the NEB method.

All structures were optimised and frequency calculations were performed to ensure the absence of any imaginary frequencies on local minima, and the presence of only one imaginary frequency on transition states. Reactants and products were re-localized starting from the transition states (IRC calculations followed by optimisations).

3. Amine influence

The amine has only a low influence on the aryl-imidate formation (**2**→**TS-1**→**4**), the values of the activation energy ranging from 14.0 to 16.9 kcal.mol⁻¹ (see Table 1). This step involves a carbon-carbon bond formation between the isocyanide and the imine carbon, which is the former carbon of the aldehyde. Thus, the amine moiety does not directly contribute to the reacting center.

Table 1. Relative activation energies (in kcal.mol⁻¹) for the reactions of several amines (n.t. = not tested).



	(A1)	(A2)	(A3)	(A4)	(A5)	(A6)	(A7)	(A8)
ΔE^\ddagger (Aryl-imidate)	15.4	14.0	14.1	15.3	16.2	14.0	16.9	14.8
ΔE^\ddagger (Smiles)	16.2	18.4	19.7	18.4	18.9	20.5	20.9	22.5
Yield (%)	n.t.	n.t.	98	n.t.	47	56	71	64




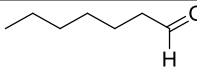
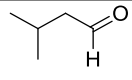
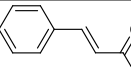
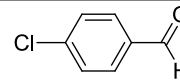
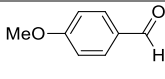
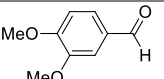
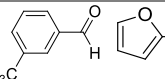



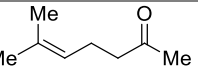
$R_1-NH_2=$	(A9)	(A10)	(A11)	(A12)	(A13)	(A14)	(A15)
ΔE^\ddagger (Aryl-imidate)	15.1	16.0	14.5	15.0	14.4	14.5	15.7
ΔE^\ddagger (Smiles)	22.4	20.7	20.3	20.5	21.2	34.6	27.9
Yield (%)	71	97	98	0	n.t.	n.t.	0

However, the nitrogen nucleophilicity plays a central role in the Smiles rearrangement (**4**→**TS-4**→**6**), and important variations are thus observed in this step (energies from 16.2 to 34.6 kcal.mol⁻¹). Except for methylamine (**A1**) for which the value is quite low (16.2 kcal.mol⁻¹), the activation energy of the rearrangement is on average 20.4 kcal.mol⁻¹ for amines from (**A2**) to (**A13**). Energies obtained for amines (**A3**) and (**A5**) to (**A11**) are consistent with experiments: all these amines behave similarly. The relatively low barrier for isopropylamine (**A4**) (18.4 kcal.mol⁻¹) points out that the reaction may be feasible with this reactant which has never been considered (due to its low boiling point). For α -substituted aryl-amines, the reaction has never been observed with methylbenzylamines (**A12**) and (**A13**) whereas the activation energy is also of 20 kcal.mol⁻¹. However, when substituted by a strong withdrawing group such as trifluoromethyl group at the benzylic position such as is (**A14**), the activation energy of the Smiles rearrangement increases significantly to 34.6 kcal.mol⁻¹. Indeed, the presence of the trifluoromethyl moiety decreases the nucleophilicity of the nitrogen atom impacting dramatically the intramolecular nucleophilic aromatic substitution. The high value obtained for the aniline (**A15**) (27.9 kcal.mol⁻¹) can explain the absence of reaction even with a pre-formed imine¹² (see Figure 5): due to conjugation with the aromatic ring, the nitrogen lone pair is less available for the S_NAr step. The derivation of some of the kinetic equations is presented in Supporting Information.

4. Carbonyl influence

Aliphatic aldehydes (**C1**) to (**C5**) have low barriers for the aryl-imidate formation (**2**→**TS-1**→**4**) (average value of 14.8 kcal.mol⁻¹) with respect to aromatic or conjugated aldehydes (**C6**) to (**C11**) (19.7 kcal.mol⁻¹ on average) and ketones (**C12**) to (**C14**) (18.1 kcal.mol⁻¹ on average) (see Table 2). This result is consistent with experimental data: aliphatic aldehydes proceed smoothly in methanol at 40°C whereas aromatic aldehydes require higher temperatures (typically 60°C) to give similar yields. During the isocyanide attack, the stabilization energy due to the conjugation of the aromatic ring with the imine is lost, increasing the barrier for the reaction of aromatic or conjugated aldehydes ((**C6**) to (**C11**)). Longer reaction times required for ketones must be related to their lower electrophilicity.

Table 2. Relative activation energies (in kcal.mol⁻¹) for the reactions of several carbonyls (n.t. = not tested).

R ₂ -CHO=							
	(C1)	(C2)	(C3)	(C4)	(C5)	(C6)	(C7)
ΔE [#] (Aryl-imidate)	15.4	13.5	15.0	15.1	15.1	21.8	18.4
ΔE [#] (Smiles)	16.2	16.6	13.5	13.2	12.8	17.1	15.7
Yield (%)	n.t.	81	98	79	98	0	80
R ₂ -CHO=							
	(C8)	(C9)	(C10)	(C11)	(C12)	(C13)	(C14)
ΔE [#] (Aryl-imidate)	20.6	20.5	18.8	18.1	19.4	17.5	17.4
ΔE [#] (Smiles)	14.5	16.6	17.8	17.3	13.5	13.8	13.9
Yield (%)	51	90	70	0	33	71	46

Among the structures presented in Table 2, cinnamaldehyde (**C6**) and furfural (**C11**) give no product under classical experimental conditions. However, furfural (**C11**) react in this coupling if Ti(O*i*Pr)₄ is added to the medium, while cinnamaldehyde (**C6**) remains inefficient.²⁶ This is consistent with the highest activation energy found with the latter for the aryl-imidate formation (21.8 kcal.mol⁻¹).

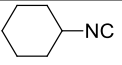

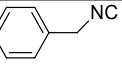
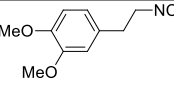
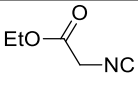
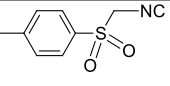
Concerning the Smiles rearrangement (**4**→**TS-4**→**6**), aliphatic aldehydes and ketones give lower values of the activation energy than aromatic aldehydes (respectively, 14.5 and 16.4 kcal.mol⁻¹ on average). As the carbonyl moiety is not directly involved in this step, small variations are observed

(from 12.8 to 17.8 kcal.mol⁻¹). Noteworthy, the lowest value (12.8 kcal.mol⁻¹) is obtained for the isovaleraldehyde (**C5**) which is considered as the most efficient partner in the Ugi-Smiles coupling. To conclude, the influence of the carbonyl reactants is mainly determinant on the aryl-imidate formation compared to the Smiles rearrangement.

5. Isocyanide influence

Besides toluenesulfonylmethyl isocyanide –TosMIC– (**I7**), isocyanides have only a little influence on the activation energy of the aryl-imidate formation (**2**→**TS-1**→**4**), even if they are involved in the reacting center (activation energies from 14.1 to 19.3 kcal.mol⁻¹, see Table 3). An activation barrier around 18 kcal.mol⁻¹ results in isocyanides of lower efficiency as attested for (**I5**) and (**I6**), although benzylisocyanide (**I4**) is a good partner in these couplings and has comparable activation energy. TosMIC (**I7**) is known to be an inefficient partner in Ugi reactions, as confirmed by the activation energy of the aryl-imidate formation. As expected for the Smiles rearrangement (**4**→**TS-4**→**6**), isocyanides have almost no influence since they are far from the reacting atoms (barrier from 14.5 to 17.3 kcal.mol⁻¹).

Table 3. Relative activation energies (in kcal.mol⁻¹) for the reactions of several isocyanides (n.t. = not tested).

R ₃ -NC=	Me-NC						
	(I1)	(I2)	(I3)	(I4)	(I5)	(I6)	(I7)
ΔE [#] (Aryl-imidate)	15.4	14.1	15.0	18.2	19.3	17.7	20.7
ΔE [#] (Smiles)	16.2	17.3	16.3	16.3	16.4	15.7	14.5
Yield (%)	n.t.	98	98	96	71	60	0

6. Phenol influence

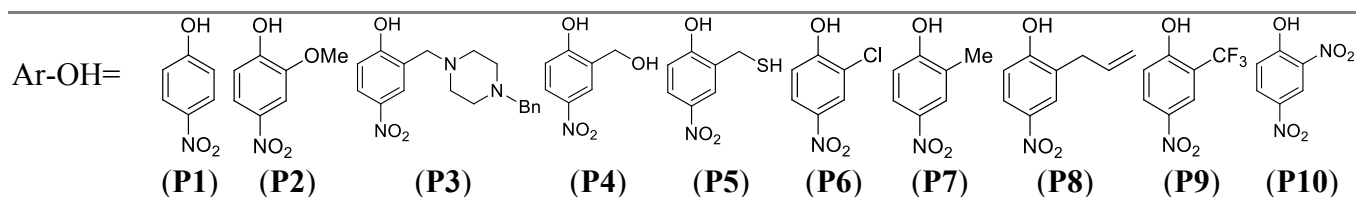
The most interesting study for Ugi-Smiles reactions relies on the phenol moiety. Depending on the phenol derivative considered, large variations are observed for the Smiles rearrangement; the barriers

for the aryl-imidate formation ($2 \rightarrow \text{TS-1} \rightarrow 4$) are however not as much influenced by the phenol. This is consistent with the mechanism presented in Figure 2 in which the acid surrogate is involved only through a hydrogen-bond during the carbon-carbon bond formation.

6.1. *Para*-nitrophenol derivatives

We first focused on *para*-nitrophenol derivatives (see Table 4). The activation energy for the aryl-imidate formation ($2 \rightarrow \text{TS-1} \rightarrow 4$) is slightly influenced by the nature of additional substituent on the aromatic core (activation energy from 14.0 to 18.6 kcal.mol⁻¹, average of 15.7 kcal.mol⁻¹). However, the Smiles rearrangement ($4 \rightarrow \text{TS-4} \rightarrow 6$) can be greatly impacted. We already demonstrated that a heteroatom at the *ortho* position (or in the alkyl chain located at the *ortho* position) can develop a hydrogen bond, lowering the activation barriers (see **(P2)**, **(P3)**, **(P5)** or **(P6)**). For 2-methyl-4-nitrophenol **(P7)** the barrier is 21.4 kcal.mol⁻¹; it decreases to 19.0 kcal.mol⁻¹ with a trifluoromethyl group **(P9)**, probably due to the additional activation by this electron-withdrawing group. The reaction may thus be possible with 2-trifluoromethyl-4-nitrophenol **(P9)**. Adding a second nitro substituent on *para*-nitrophenol (**(P1)** to **(P10)**) lowers both the aryl-imidate formation and the Smiles rearrangement barriers by 2 kcal.mol⁻¹, but also lowers the yield which is surprising. This can be due to the lack of stability of the aryl-imidate made from **(P10)** which can thus be methanolysed. Another explanation is the low solubility of 2,4-dinitrophenol at high concentrations. It must be pointed out that it is difficult to extract general rationalization from such data, since the activation energy of efficient phenols (19.5 kcal.mol⁻¹ for **(P1)** for example) can be higher than the activation energy of inefficient ones (18.2 kcal.mol⁻¹ for **(P8)** for example).

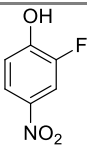
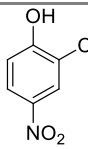
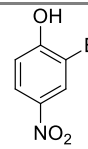
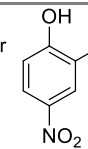
Table 4. Relative activation energies (in kcal.mol⁻¹) for the reactions of several phenols (n.t. = not tested).



ΔE^\ddagger (Aryl-imidate)	16.9	16.6	14.0	18.6	12.7	14.0	16.9	17.2	14.2	13.6
ΔE^\ddagger (Smiles)	19.5	17.7	11.5	14.8	20.3	18.5	21.4	18.2	19.0	14.2
Yield (%)	98	62	88	n.t.	n.t.	95	0	0	n.t.	73

The study of the influence of a heteroatom at the *ortho* position was then extended to halogen atoms. The four activation energies are similar for both the aryl-imidate formation (**2**→**TS-1**→**4**) (average of 13.7 kcal.mol⁻¹) and the Smiles rearrangement (**4**→**TS-4**→**6**) (18.8 kcal.mol⁻¹). The low halide influence can be attributed to a compromise between the hydrogen bond strength and the ring activation, the former being more important with heavy halides whereas the latter is less important.^{27,28}

Table 5. Relative activation energies (in kcal.mol⁻¹) for the reactions of several phenols (n.t. = not tested).

Ar-OH=				
	(P11)	(P6)	(P12)	(P13)
ΔE^\ddagger (Aryl-imidate)	13.5	14.0	14.8	12.4
ΔE^\ddagger (Smiles)	19.3	18.5	18.4	19.1
Yield (%)	n.t.	95	n.t.	95 ^a

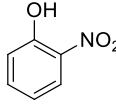
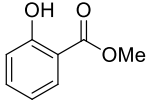
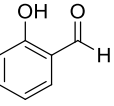
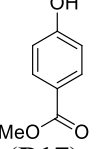
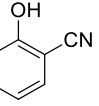
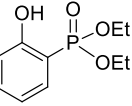
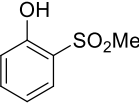
a) In that specific case, the classical experimental conditions was inefficient and only a 10:1 mixture of toluene/water with NH₄Cl as solvent could lead to the desired product.²⁹

6.2. Aromatic ring activation

The influence of activating substituents was compared (see Table 6). *Ortho*-nitrophenol (**P14**) has slightly lower activation energies than *para*-nitrophenol (**P1**), but similar efficiency in the coupling. As expected, an ester is less efficient to activate the aromatic ring than the nitro group ((**P15**) and (**P17**)). The activation energy of the Smiles rearrangement for methyl *ortho*-hydroxybenzoate (**P15**) is of 18.3 kcal.mol⁻¹ whereas it is of 22.4 kcal.mol⁻¹ for the *para* derivative (**P17**) probably due to an intramolecular hydrogen bond with the ester moiety at the *ortho* position. These results are consistent with experiments since the reaction proceeds with (**P15**) but not with (**P17**). *Ortho*-hydroxybenzaldehyde (**P16**) is not efficient in the Ugi-Smiles coupling even if the energy barriers are

relatively low; this can be explained by side-reactions.³⁰ It can however be seen that the activation of the phenyl ring by an aldehyde is stronger than the one from a nitro group. *Ortho*-cyanophenol (**P18**) and *ortho*-phosphonate-phenol (**P19**) are not efficient partners in Ugi-Smiles couplings, which can be correlated to high values found for the Smiles activation energies (22.9 and 20.4 kcal.mol⁻¹ respectively). Even if the Smiles rearrangement cannot proceed, it could be possible to form the aryl-imidate and isolate these structures since the first activation energy is of 17.3 kcal.mol⁻¹ for (**P18**) (see Figure 4 and (**P31**) below). The inefficiency of this coupling can again be due to the low stability of the aryl-imidate which can be solvolysed or react on silica gel. Sulfones have never been tested in Ugi-Smiles couplings. However, the low barrier observed (19.0 and 17.8 kcal.mol⁻¹ for (**P20**)) suggests that they could be good partners for this reaction.

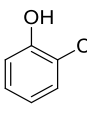
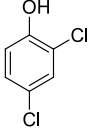
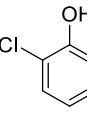
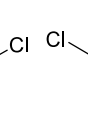
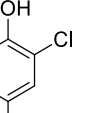
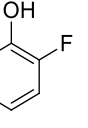
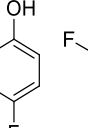
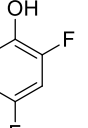
Table 6. Relative activation energies (in kcal.mol⁻¹) for the reactions of several phenols (n.t. = not tested).

Ar-OH=							
	(P14)	(P15)	(P16)	(P17)	(P18)	(P19)	(P20)
ΔE^\ddagger (Aryl-imidate)	15.4	20.1	19.3	20.5	17.3	22.7	19.0
ΔE^\ddagger (Smiles)	16.2	18.3	15.4	22.4	22.9	20.4	17.8
Yield (%)	96	76	0	0	0	0	n.t.

When simply activated by halogen atoms, the corresponding phenols do not undergo the desired reaction. Interestingly, the formation of the aryl-imidate intermediate (structure (**4**) in Figure 2) is strongly influenced by the number of chlorine atoms and by their positions in the aromatic ring: the activation energy decreases from 20.2 to 15.9 kcal.mol⁻¹ when chlorine atoms are added ((**P21**) to (**P24**)) (see Table 7). The barrier for the Smiles rearrangement (**4**→**TS-4**→**6**) is always relatively high (26 kcal.mol⁻¹). Fluorine atoms are not activating enough to allow the aryl-imidate formation and the

final rearrangement (see Table 7), even with perfluorophenol (**P28**) whose Smiles activation energy is still too high to be crossed (25.5 kcal.mol⁻¹).

Table 7. Relative activation energies (in kcal.mol⁻¹) for the reactions of several phenols (n.t. = not tested).

Ar-OH=								
	(P21)	(P22)	(P23)	(P24)	(P25)	(P26)	(P27)	(P28)
ΔE^\ddagger (Aryl-imidate)	20.2	18.9	16.0	15.9	21.7	23.7	17.5	15.6
ΔE^\ddagger (Smiles)	26.9	26.1	26.6	26.0	28.2	30.3	29.9	25.5
Yield (%)	0	0	n.t.	0	0	n.t.	n.t.	0

6.3. Thiophenol derivatives

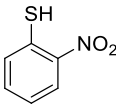
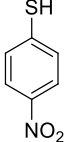
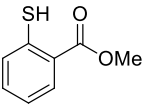
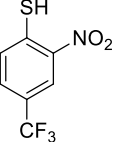
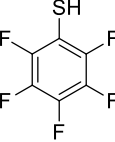
A general observed trend is that the more acidic is the phenol, the more efficient is the activation of the imine through a hydrogen-bond interaction, lowering the activation energy of the aryl-imidate formation. The pK_as of thiophenols being lower than the one of phenols, the barriers for the aryl-imidate formation are consequently lower for mercapto compounds than for hydroxyl derivatives: 10.9 vs 16.8 kcal.mol⁻¹ on average (see Table 8).

For the Smiles rearrangement (**4**→**TS-4**→**6**), the activation energy of the 4-nitrothiophenol (**P30**) is too high to be crossed (19.8 kcal.mol⁻¹) which explains why almost no product is observed with this acid (see Figure 3). Noteworthy, the Smiles rearrangement barrier is much lower for the 2-nitrothiophenol (**P29**) (13.1 kcal.mol⁻¹) and the reaction may proceed in that case; this is experimentally observed with (**P32**), which gives the desired adduct in 30% isolated yields. A possible explanation for the deceiving results obtained with thiophenols relies on side-reactions which can occur in the medium such as the hydrolysis or methanolysis of the aryl-imidate intermediate,³¹ or the reaction with free radicals formed *in situ*.

Surprisingly, methyl thiosalicylate (**P31**) affords the aryl-imidate (**4**) (see Figure 4). This result can be explained by the low barrier for the first step (11.1 kcal.mol⁻¹) associated with a high barrier for the

Smiles rearrangement (19.6 kcal.mol⁻¹), trapping the process in an energy well at the stage of the aryl-imidate intermediate (**4**), in agreement with the experiments.¹⁵ Finally, with a value of 30.8 kcal.mol⁻¹ for the pentafluorothiophenol (**P33**), the Smiles rearrangement cannot proceed and the aryl-imidate intermediate (**4**) could probably be isolated.

Table 8. Relative activation energies (in kcal.mol⁻¹) for the reactions of several thiophenols (n.t. = not tested).

Ar-OH=					
	(P29)	(P30)	(P31)	(P32)	(P33)
$\Delta E^\ddagger(\text{Aryl-imidate})$	10.5	10.4	11.1	10.3	11.4
$\Delta E^\ddagger(\text{Smiles})$	13.1	19.8	19.6	12.9	30.8
Yield (%)	n.t.	<10	84 ^a	30	n.t.

a) In that specific case, the isolated compounds is the aryl-imidate (**4**) which has not undergone the Smiles rearrangement.

7. Conclusion

In the present article, we have studied the substituent effects on the aryl-imidate formation and on the Smiles rearrangement of the Ugi-Smiles reaction. Even if it is not possible to directly correlate the yields to the activation energies, most of the experimental results have been explained and general trends emerged. The amines mainly influence the Smiles rearrangement, whereas the carbonyl variations can be explained with the aryl-imidate formation. The isolation in some cases of the intermediate aryl-imidate can be rationalized by the comparison of both activation energies of the two steps. However, it remains unclear why the aryl-imidate is seldom obtained. Though some of the results with phenols may seem contradictory with the experimental work, one must not forget all the side reactions and solubility problems that may be encountered on these systems. Most interestingly, this theoretical study has highlighted the potential of activating groups such as sulfones which have not been previously tested. For such groups, our results will certainly be a strong incentive to go beyond the efforts needed for the preparation of the starting materials.

SUPPORTING INFORMATION: Complete list of authors for Ref. 16. Detailed energy profile of the Ugi-Smiles reaction. Kinetics of some illustrative reactions. Gibbs free energies of activation for all the reactions studied in the article. List of the partners used to obtain the best yield for each variation. Cartesian coordinates of some structures discussed in the text. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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SYNOPSIS TOC:

