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Passerini-Smiles reaction of α -ketophosphonates: a platform to unveil new Phospha-Brook/Smiles embedded cascades.

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Dedication ((optional))

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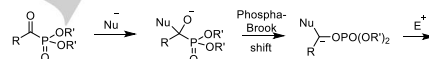
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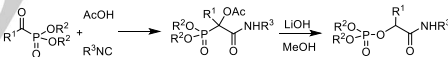
Abstract: α -ketophosphonates are suitable starting materials for Passerini-Smiles reactions with nitrophenols. Under treatment with bases, the resulting adducts offer opportunities to observe complex cascades involving multiple Smiles transfers coupled with Phospha-Brook rearrangement. When using 4-nitrophenols a rare 1,4-Truce-Smiles is observed leading to diarylacetonitrile derivatives while 2-nitroderivatives lead to a completely different reactivity pattern with a probable conversion of the nitro into a nitroso intermediate. DFT calculations have been performed on both families of adducts to support the proposed mechanisms. The potential of this work has been further demonstrated by the use of N-aryl α -ketoamides as alternative starting materials for these cascades as well as the disclosure of a new aza-Nazarov access to hydroxy-indolones.

to an efficient PB rearrangement under saponification conditions (Scheme 1, B).

A) Phospha-Brook rearrangement from α -ketophosphonates:



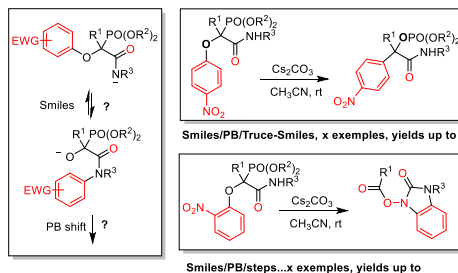
B) Passerini reaction of α -ketophosphonates:



C) Passerini-Smiles reaction:



D) This work



Scheme 1. Passerini reaction of α -ketophosphonate followed by Phospha-Brook (PB) rearrangement.

Introduction

α -ketophosphonates, easily obtained under treatment of acyl chlorides with alkylphosphites, represent a very versatile class of ketones.^[1] Beside the classical reactivity of a ketone with enhanced electrophilic behavior, these compounds may be further involved in carbon to oxygen migration of the phosphorus group (Phospha-Brook rearrangement)^[2] after nucleophilic additions onto the ketone. Indeed, various nucleophiles such as cyanide anion have been explored in order to achieve efficient C-C bond forming strategies based on Phospha-Brook (PB) shift followed by trapping of the resulting carbanion with electrophiles (Scheme 1, A).^[2] Several years ago, we have shown that α -ketophosphonates could be involved in Passerini reaction without inducing any PB shift despite the stabilizing effect of the intermediate nitrilium on the potential final carbanion.^[3] This may be explained by the acidic conditions required for the Passerini reaction to occur as the Passerini adducts could effectively lead

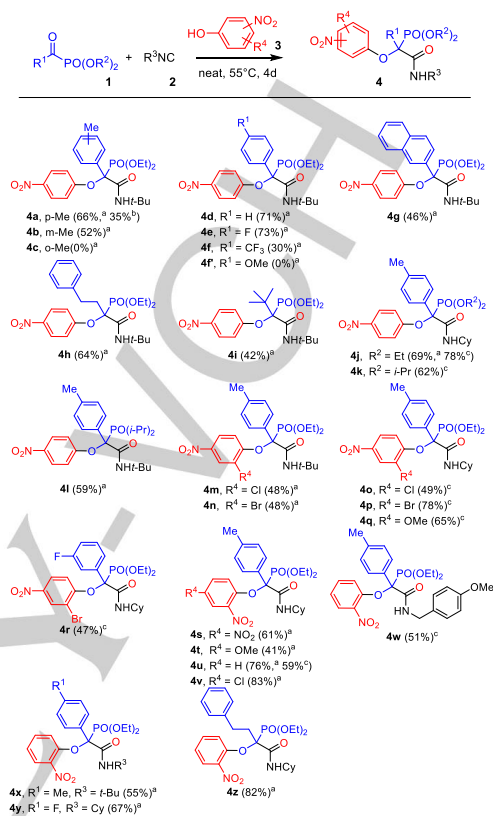
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Following our disclosure of enhanced conditions for the Passerini/Smiles reaction (Scheme 1, C),^[4] we became interested in the ability of α -ketophosphonates to act as efficient carbonyl partner in this reaction with the objective of using a PB shift to displace any potential Smiles transfer between the amide and the oxygen of the phenolic Passerini-Smiles adduct (Scheme 1-D). We now wish to disclose the results of this study showing a surprising reactivity difference observed when using 4 and 2-nitrophenols, some rare 1,4-Truce-Smiles shifts and undisclosed fragmentation/cyclization of nitroso intermediates (Scheme 1, D).

Results and discussion

4-Tolyl-diethylketophosphonate **1a** was selected for the first steps of this study. It was easily obtained in quantitative yield under addition of diethylphosphite to 4-tolyl chloride at room temperature. Though aryl ketones are known as poorly reactive partners in Passerini-Smiles reactions,^[4] the choice of an aromatic ketophosphonate was expected to make the following Phospha-Brook rearrangement much easier to observe than in the case of alkylketophosphonates. However, we could still observe a three-component coupling using stoichiometric amounts of ketophosphonate **1a**, *t*-butyl isocyanide **2a** and 4-nitrophenol under prolonged heating for four days at 55°C. The Passerini adduct **4a** was then obtained in a low 35% yield under neat condition (Scheme 2). We could raise the yield up to 66% by increasing the amount of the slightly volatile *t*-butylisocyanide up to 3 equiv. For less volatile isocyanides such as cyclohexyl isocyanide **2b**, 1.5 equivalent were enough to ensure a good 78% yield of adduct **4j** in the reaction between **1a** and 4-nitrophenol. In this latter case, performing the reaction with a small amount of solvent (THF, 5M) was found beneficial in term of solubility and viscosity of the reaction medium. With these two conditions in hand, a set of 26 Passerini adducts **4a-4z** were prepared from *t*-butyl, cyclohexyl and methoxybenzyl isocyanides possessing an ortho or para nitro substitution pattern (Scheme 2). 2 and 4-nitrophenols showed a comparable reactivity towards isocyanides and ketophosphonates and, as expected, we observed a slightly higher reactivity in the formation of Passerini adducts prepared from aliphatic ketophosphonates (**4h**, **4i** and **4z**), compared to analogous aryl substituted ketophosphonates. For the latter, lowering the electrophilicity of the ketophosphonate using a 4-methoxy substituent didn't allow anymore the 3-component reaction to proceed even under higher temperature (failed synthesis of **4f**, scheme 2).

With these Passerini adducts in hand, we next examined the ability to perform Smiles/Phospha-Brook cascades starting with **4a**. When **4a** was treated with 0.5 equiv. of Cs₂CO₃ in THF, we were delighted to observe within one hour at room temperature the formation of diarylacetylide **5a** together with N-nitroaryl amide **6a** (Table 1, entry 1). Working with different solvents and bases allowed us to obtain two different set of conditions for high yielding formation of **5a** and **6a**. When DBU was used in acetonitrile, the N-aryl **6a** was formed in 84% yield, whereas the more basic Cs₂CO₃ afforded the diaryl **5a** in a quantitative yield (95% isolated yield).



a) reaction performed with 1 equiv. of **1** and **3** and 3 equiv. of **2**. b) reaction performed with 1 equiv. of **1**, **2** and **3**. c) reaction performed in THF (5M) with 1 equiv. of **1** and **3** and 1.5 equiv. of **2**.

Scheme 2. Passerini reactions of α -ketophosphonates.

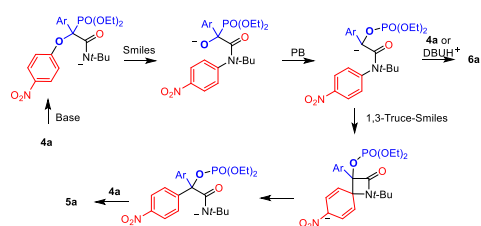
Table 1. Optimized conditions for the formation of **5a**.

Entry	Base (equiv.)	Solvent	5a ^a	6a ^a	4a ^a
1	Cs ₂ CO ₃ (0.5)	THF	58	27	13
2	Cs ₂ CO ₃ (0.5)	Toluene	-	-	87
3	Cs ₂ CO ₃ (0.5)	Ethanol	48	29	-
4	Cs ₂ CO ₃ (0.5)	DMSO	83	-	-
5	Cs ₂ CO ₃ (0.5)	CH ₃ CN	95 ^b	-	-
6	<i>t</i> -BuOK (0.5)	CH ₃ CN	78	-	-
7	NaH (0.5)	CH ₃ CN	55	-	-
8	DBU (0.5)	CH ₃ CN	5	84	-
9	Cs ₂ CO ₃ (1.5)	CH ₃ CN	81	-	-
10	Cs ₂ CO ₃ (0.2)	CH ₃ CN	90	-	-

a) NMR yield using 1,3,5-trimethoxybenzene as internal standard. b) Isolated yield.

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The room temperature high yielding formation of **5a** is particularly remarkable. Together with the creation of a new C-C bond leading to diarylacetate derivatives, the transformation displays a formal migration of an oxygen atom within the molecule. Amide **6a** gives us some indications for a possible reaction mechanism involved in the conversion of **4a** into **5a**. Indeed, the structure of **6a** suggests that after deprotonation, starting **4a** undergo a Smiles rearrangement^[6] followed by the expected Phospha-Brook shift (Scheme 3). The resulting anion may be re-protonated to afford **6a** or react via a further Truce-Smiles shift leading to **5a**.



Scheme 3. Plausible Smiles/Phospha-Brook/Truce-Smiles cascade supporting the formation of **5a**.

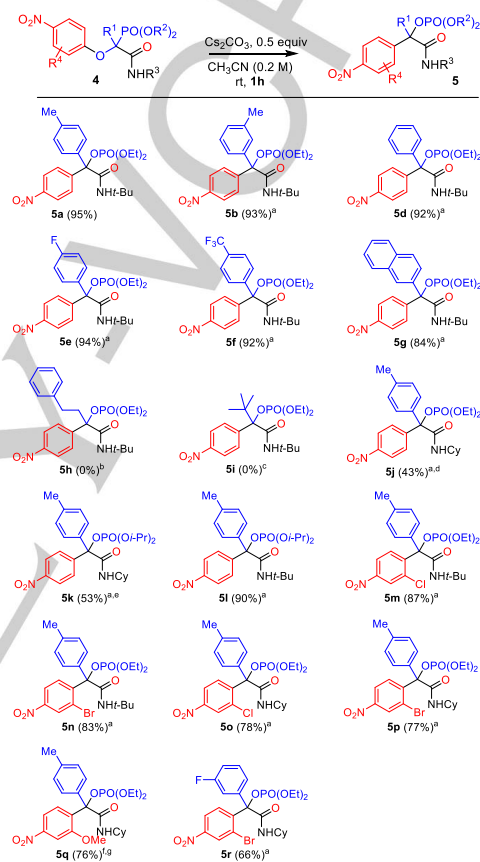
Truce-Smiles reactions are intramolecular aryl shifts from a heteroatom to a carbanionic center. As the Smiles rearrangement, the reaction classically involves a spirocyclic anionic intermediates of medium ring size leading to 1,4 or 1,5 aryl shifts.^[6] Due to competing β -elimination, 1,3-Truce-Smiles rearrangements are much less documented appearing only in few reports with thus little know data about the structural requirements for the rearrangement to occur.^[7]

In our case, the fact that **6a** remained unaffected when placed under the optimized conditions for the formation of **5a** shows that the protonation step after the Phospha-Brook rearrangement is not reversible under the conditions of the reaction. Increasing the temperature or the strength of the base led to complex mixtures without formation of **5a**. With these data and mechanistic considerations in mind, the scope of the transformation was then evaluated using the various Passerini adducts **4** prepared from 4-nitrophenols (Scheme 4).

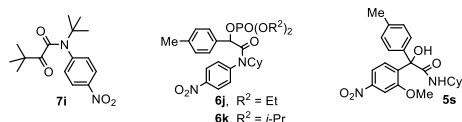
The results obtained show that an aryl group at the α -amide position is needed for the cascade to occur. Passerini adducts **4h** and **4i** prepared from aliphatic oxophosphonates both failed to afford the expected amides **5h** and **5i**. In the case of **4i**, a complex mixture is obtained whereas the formation of **7i** from **4i** indicates that after the first Smiles rearrangement, the Phospha-Brook shift failed to occur due to a lower stabilization of the amide enolate together with a competing retro-Pudovik process. The steric hindrance around the reactive centers does not seem to disturb the process and may even has a beneficial effect. Indeed, *N*-*t*-butyl amides give the best yields while the process is less efficient for cyclohexyl amides.

The case of **4j** is particularly interesting. Under the optimized conditions for **5a**, the low yielding formation of **5j** along with Smiles/PB amide **6j** may be explained by a less efficient Truce-Smiles shift leading to a faster protonation of intermediate amide enolate towards **6j**. Indeed, a lower Thorpe-Ingold effect brought by the cyclohexyl group would make the 4-membered spirocyclic ring more difficult to obtain when compared with the tert-butyl

group. In support of this analysis, raising the steric hindrance either by using 4-nitrophenol substituted at the 2 position (**5o**, **5p**, **5s**) or replacing the diethyl phosphonate by a diisopropyl phosphonate moiety (**5k**) restores good yields for cyclohexyl amides. In the case of **4q**, the expected phosphate **5q** is destabilized by the ortho methoxy group and the phosphate is replaced by water under column chromatography leading to **5s** with a good 74% isolated yield.



a) isolated yields. b) hydrocinnamaldehyde. c) **7i** (62%) was only isolated. d) **6j** (34%) was isolated as side-product. e) **6k** (26%) was isolated as side-product. f) NMR yield using 1,3,5-trimethoxybenzene as internal standard. g) **5s** (74%) was only isolated.



Scheme 4. Scope of the Smiles/Phospha-Brook/Truce-Smiles cascade.

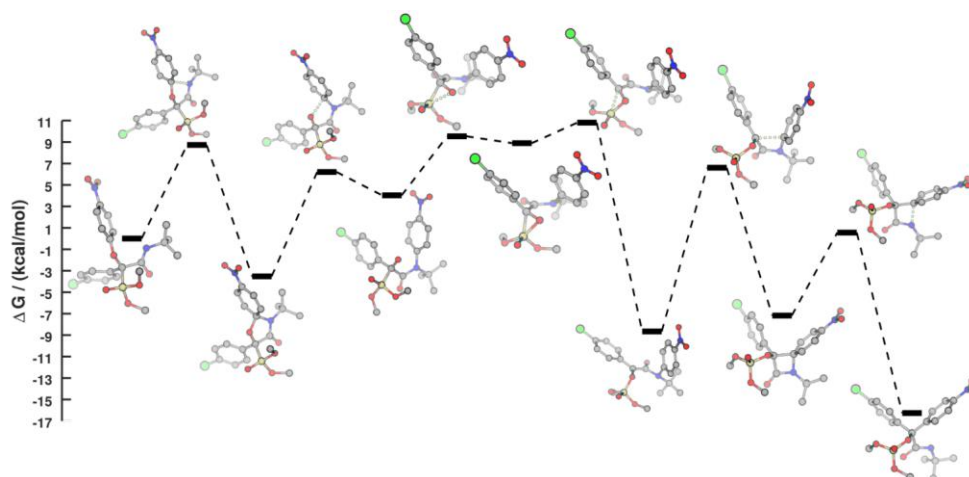
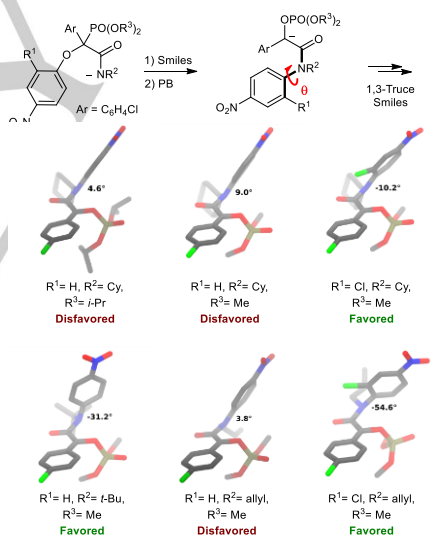


Figure 1. Free enthalpy profile associated to the rearrangements of Passerini-Smiles adducts **4** into phosphates **5**. H atoms are hidden for the sake of clarity. Calculations performed at the M06-2X/6-31G(d,p) level using PCM as implicit solvation model for the acetonitrile.

In order to bring additional information on the structure/reactivity relationship of these adducts and confirm our proposed mechanism, quantum chemistry calculations were performed using density functional theory (DFT) on a model system. The whole sequence was modelled at M06-2X/6-31G(d,p) level and solvent influence was considered by means of PCM approximation (Figure 1).

The resulting free energy profile showcased a thermodynamically favored transformation with a global free energy decrease of 17 kcal.mol⁻¹. Additionally, the elementary step associated to the formation of the 4-membered spirocyclic intermediate could be identified as the rate determining step for this sequence with an activation barrier of 15 kcal.mol⁻¹. Secondly, 1,3 Truce-Smiles sequences were computed for a series of differently substituted amide enolates, and their geometries were compared (Scheme 5). Free energy variations during the formation of the spirocyclic adduct were correlated with the orientation of the nitroarene towards the carbanion, which is mainly characterized by dihedral angle θ and could be analyzed in two trends (see *Supporting Information* for complete energy profiles). In opposition with our first hypothesis around steric hindrance and Thorpe-Ingold effects, the effect of the substituent on the distance between the reactive centers does not praise for an important Thorpe-Ingold effect. However important changes were observed in the dihedral angles associated to the rotation of the N-Aryl bond of the intermediate anion before Truce-Smiles rearrangement (Scheme 5). While the cyclohexyl group gives an angle less favorable to an interaction of the anion with the π orbitals of the nitroaryl compared ($\theta = 9^\circ$ versus -31° for a N-*t*-Butyl), a better geometry is restored when a substituent is added at the ortho position of the nitroaryl. This effect should be further increased by replacing the cyclohexyl group by a less sterically demanding allyl moiety (see SI part for further discussion).



Scheme 5. Geometries obtained for model compounds at M06-2X/6-31G(d,p) level. Main geometrical parameter controlling the efficiency of the Truce-Smiles rearrangement highlighted in green when favored and red when disfavored.

After studying the behavior of 4-nitrophenols derived Passerini-Smiles adducts, we next examined the use of 2-nitrophenol derivatives. Smiles processes are known to be more efficient with 2-nitrophenols than 4-nitrophenols^[9] and we showed that ortho substitution on the phenol moiety is compatible with the Smiles/PB/Truce-Smiles cascade (scheme 4, **5m-5r**). However, a completely different and more complex cascade was observed

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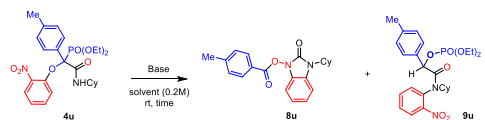
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when submitting **4u** under our optimized conditions for **5a** (Table 2).

In contrast with the previous cascade completed within one hour, the reaction was much slower at room temperature leading after 18 hours to the new benzimidazolone **8u** obtained in 40% yield with 40% remaining starting material. The lack of the phosphate group in **8u** together with unreacted **4u** praise for the use of higher amount of base to complete the reaction. Indeed, raising the amount of base to 1,1 equiv. allowed us to reach a quantitative formation of **8u** after 12 hours at room temperature. As observed for diarylamides **5**, Cs₂CO₃ and acetonitrile remain the best base/solvent system for this new transformation (Table 2).

Table 2. Benzimidazole **8u** formation and optimization.^a



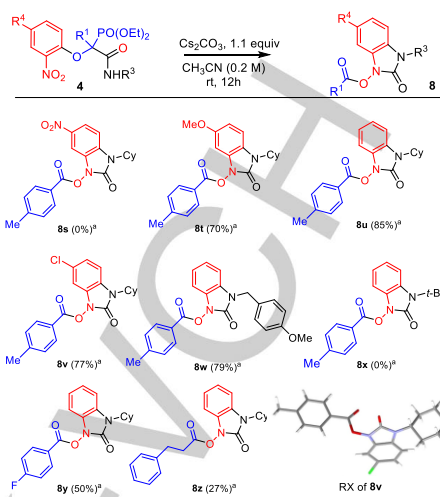
Entry	Base (equiv.)	Solvent	8u ^d	9u ^d	4u ^d
1	Cs ₂ CO ₃ (0.5)	CH ₃ CN	34	-	49
2	Cs ₂ CO ₃ (1.1)	CH ₃ CN	50	-	48
3	Cs ₂ CO ₃ (1.1)	Ethanol	31	-	-
4	Cs ₂ CO ₃ (1.1)	DMF	60	-	-
5	Cs ₂ CO ₃ (1.1)	THF	44	7	15
6	Cs ₂ CO ₃ (1.1)	DMSO	48	-	-
7	<i>t</i> -BuOK (1.1)	CH ₃ CN	56	-	-
8	DBU (1.1)	CH ₃ CN	30	22	-
9 ^b	Cs ₂ CO ₃ (1.1)	CH ₃ CN	quant	-	-
10 ^c	Cs ₂ CO ₃ (1.1)	CH ₃ CN	56	-	-

a) Reaction conditions: 3 hours at rt. b) Optimized conditions: 12 hours at rt. c) 3 hours at 50°C. d) NMR yield using 1,3,5-trimethoxybenzene as internal standard.

In the case of DBU as a base or methanol as solvent, small amounts of Smiles/PB amide **9u** were also obtained as side-product. These new optimized conditions were further applied to 2-nitro Passerini-adducts of Scheme 2 and the results displayed in Scheme 6.

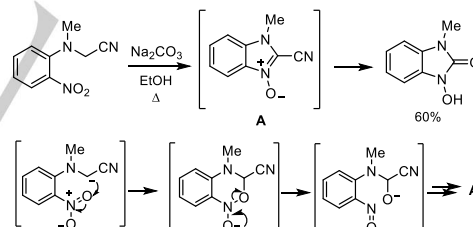
This new cascade is not observed using *N*-*t*-Butyl amides as starting materials but less bulky cyclohexyl or benzyl groups are well tolerated. The low yielding formation of benzimidazolones **8z** may be associated with a less efficient PB shift as observed for 4-nitroderivatives (scheme 4, **5h**). Considering the complex transformation involved in this reaction, we were happy to confirm the structures of these adducts by a single crystal X-Ray crystallography performed on **8v** (scheme 6).

The substitution pattern of the final benzimidazoles is consistent with a first Smiles rearrangement followed by a PB shift as observed in the formation of **5a**. The ortho nitro group must then interact with the amide enolate leading to carbon-nitrogen bond formation faster than the previous Truce-Smiles rearrangement. The closest *N*-hydroxy-benzimidazole formations reported in the literature may be found in the studies of Tennant and Smith who examined the formation of *N*-hydroxy-benzimidazolones from *N*-cyanomethyl-*o*-nitroanilines (Scheme 7).^[10] They proposed a reaction mechanism involving the formation of a 6-membered ring cyclic intermediate leading to a formal intramolecular redox process with conversion of the nitro into a nitroso group. The resulting cyano-benzimidazoles are known to be easily hydrolyzed into benzimidazolones under basic conditions.^[11]



Scheme 6. Scope for the synthesis of benzimidazolones starting from Passerini adducts derived from 2-nitrophenols; a) isolated yields.

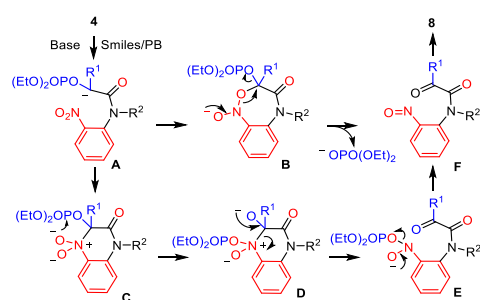
Even though our reaction is more complex, the final structure obtained praise for the formation of a nitroso intermediate as proposed by Smith in their benzimidazolones synthesis.^[10] The oxygen transfer from the nitro group would lead to nitroso-ketoamide **F** as key intermediate with parallel elimination of the phosphate moiety (Scheme 8).



Scheme 7. previous Nitro-benzimidazole conversion

Two pathways may be considered for the nitroso formation according to the chemo-selectivity of the enolate attack: formation of a 7-membered ring cyclic intermediate **B** through attack on the O atom of the nitro group or attack onto the nitrogen atom leading to **C**^[12] followed by phosphate transfer, ketoamide formation and phosphate elimination.

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Scheme 8. Possible steps towards nitroso intermediate F

The final conversion of F into 8 is more problematic with a formal σ - π metathesis leading to an insertion of the nitroso moiety into the C-C bond of the ketoamide, a reaction which has no precedent in the literature. Even though several fragmentations of α -dicarbonyl compounds have been reported,^[13] none may be adapted to explain the fragmentation observed herein.

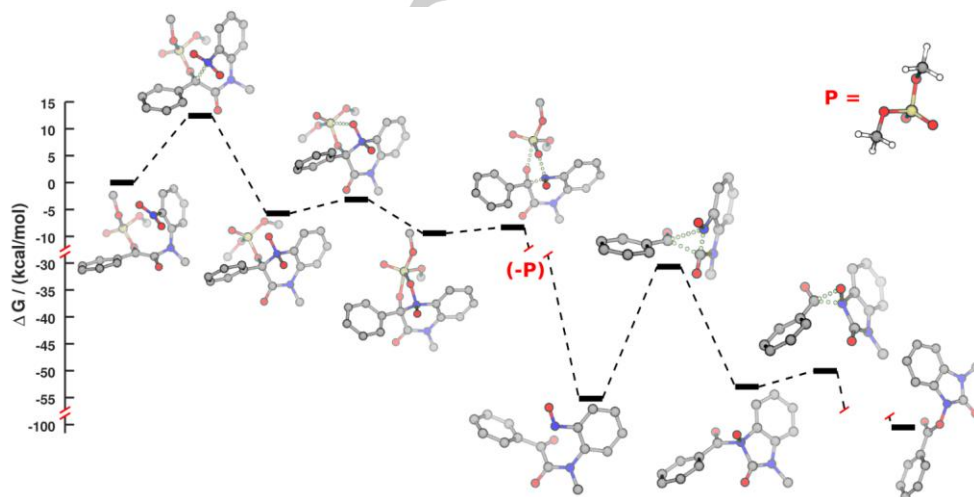
Additional quantum chemistry calculations employing same calculation level were performed starting from a model substrate for (A), with the goal to discriminate between the two pathways suggested in scheme 8 and propose a sequence for the formation of 8 from nitroso intermediate F (Figure 2).

Whereas no local minimum accounting for structure B could be reached starting from the amide enolate A, structure C was

of compound A. Formation of this 6-membered ring appeared to be a favorable process with an activation barrier of only 12 kcal.mol⁻¹. The formation of nitroso F starting from C proceeded favorably from a thermodynamic point of view through a two-step sequence with the intermediate formation of a pentacoordinate phosphacycle. The following fragmentation of the latter led to a phosphate shift with concomitant nitroso formation and phosphate elimination. The important free energy decrease observed during the fragmentation step E \rightarrow F is partly explained by the entropic gain associated with the departure of a phosphate anion in this elementary step.

The conversion of F into 8 proceeds through a two-step sequence. First, insertion of the nitrogen atom of the nitroso group in the C-C bond of the α -ketoamide is observed with an activation energy of 25 kcal.mol⁻¹. The resulting zwitterionic intermediate gives 8 by a 1,2 migration of the benzoyl moiety.

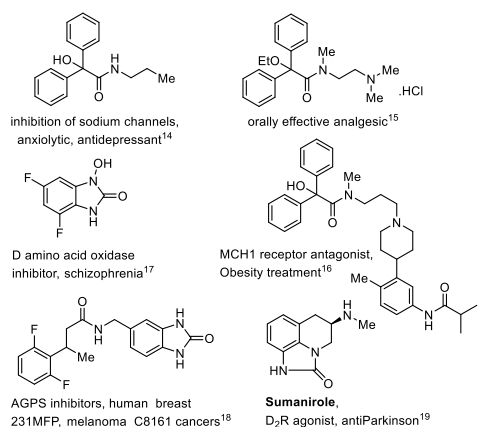
Starting from 2- and 4-nitrophenols, these two different cascades afford a fast access to diarylacetyl amides and N-hydroxybenzimidazolone derivatives. These two families of compounds display important biological activities. Hydroxy and alkoxy-diarylamides have been proposed as potential drugs with anxiolytic^[14], analgesic properties^[15] or for obesity treatment.^[16] If N-hydroxy-benzimidazoles have been associated with limited biological activities such as a potential use for treatment of schizophrenia, however their reduced benzimidazoles analogues have been widely used in medical chemistry. Scheme 10 displays some structures belonging to these families together with their reported activities.



localized on the free energy surface 5 kcal.mol⁻¹ below the energy

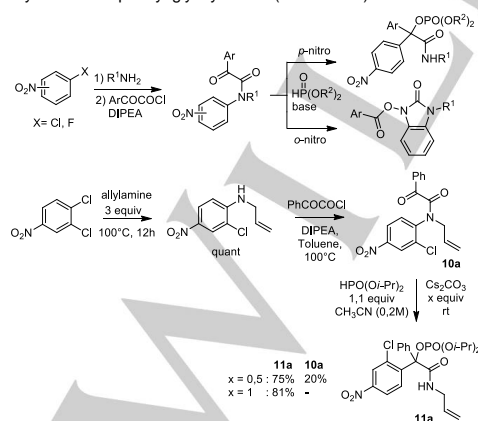
Figure 2. Free enthalpy profile associated to the rearrangement of Passerini-Smiles adducts 4 into benzimidazolones. Calculations were performed on the M06-2X / 6-31G (d,p) level and solvent was implicitly modelled using PCM solvation model. (-P) stands for the departure of phosphate anion.

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Scheme 10.

Despite these medicinal applications and the efficiency of the Smiles based cascades to reach these derivatives, it is possible to argue that the synthetic potential of the overall process is reduced by a first Passerini-Smiles step displaying moderate yields, long reaction time and limited availability of starting isocyanides. With these elements in mind, we decided to search for alternative starting materials that we could engage in similar cascades and became interesting by the potential use of a Pudovik reaction of N-aryl α -ketoamides.^[20] Indeed, dialkylphosphite addition to the latter would form an intermediate hydroxy-phosphonate that would directly evolve towards further PB/Smiles or PB/Nitro-nitroso cascade (Scheme 11). The starting materials are easily prepared by N-arylation of primary amines using chloro- or fluoro-nitroaromatics followed by acylation with α -ketoacyl chlorides.^[21] Thus, N-arylnitroketoamide **10a** was prepared in 97% yield from 1,2-dichloro-4-nitrobenzene, allylamine and phenyl glyoxylic acid (Scheme 11).

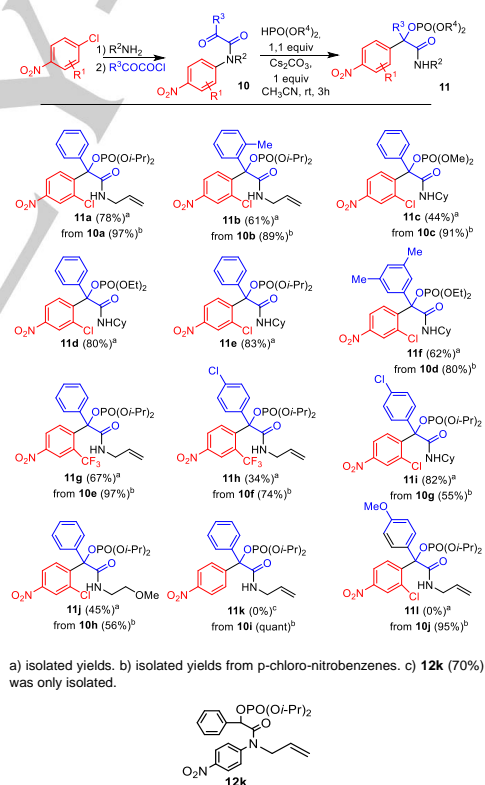


Scheme 10. Pudovik/PB/Truce-Smiths cascades with nitroaromatics

As dialkylphosphites additions onto carbonyl derivatives are efficiently catalyzed by various bases,^[20] the optimized conditions

for the conversion of **4** into **5** were directly tested in an attempt to observe under the same set of conditions both the Pudovik reaction and the following PB/Truce-Smiths cascade. Indeed, we were delighted to observe the direct conversion of **10a** into **11a** isolated in 75% yield after 3h at rt (Scheme 11). It could be raised to 81% using one equivalent of Cs₂CO₃ for faster Pudovik coupling.

A set of various aryl-ketoamides **10** was then transformed into diarylacetamides allowing to further confirm the power of this PB/1,3-Truce-Smiths pathway for new C-arylations (Scheme 12). Interestingly, this synthetic pathway allows to extend the scope of the previous route allowing substitution patterns that were not compatible with the Passerini-Smiles step. Indeed, when arylketophosphonates **1** were sterically hindered at the carbonyl position using ortho-substituent on the aryl ring, we could not observe any Passerini-Smiles coupling. However analogous phosphate such as **11b** could be easily obtained under a Pudovik/PB/Truce-Smiths cascade. Despite the moderate yield obtained, the formation of **11e** is most noteworthy due to the high steric hindrance brought by both ortho substituted aryl and diisopropylphosphate moiety. Finally, the results obtained further confirm the importance of ortho substitution at the nitroaryl ring (Scheme 11, **11k**), and support the DFT calculations performed for N-allyl derivatives (see Scheme 5).

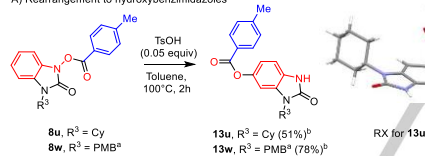


Scheme 11. Scope of the Pudovik/PB/Truce-Smiths cascade

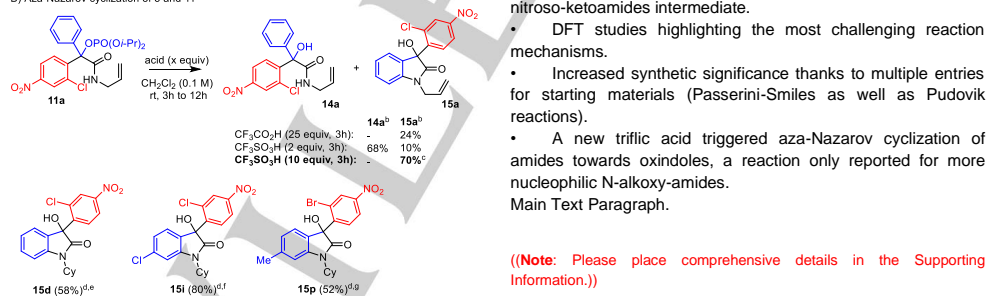
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Besides their interest as potential drug candidates, the two families of products obtained in these new PB/Truce-Smiles cascades may be further transformed in a single step to products of higher medicinal potential. Dealing with *N*-hydroxy-benzimidazole derivatives, well known rearrangement of *N*-hydroxy-anilines towards phenol derivatives may be easily observed leading to highly functionalized hydroxy-benzimidazoles with high yield (Scheme 12, A).^[22] In the case of bisarylacetamides, we surmised that the benzylic phosphate moiety could act as a potential leaving group under proper acidic activation, leading to Nazarov type cyclization^[23] or intermolecular trapping with nucleophiles.^[24] Due to the strong inhibiting effect brought by nitroaryl group, we envisioned that such reaction would require strongly acidic conditions. Indeed, when **11a** was treated with trifluoroacetic acid at room temperature or at higher temperature, we could only observe the formation of the hydroxy-analogue **12a** without any cyclisation (*à vérifier, yield...., Scheme 12, B*). However, under treatment with triflic acid in excess, we could observe a cyclization leading to the new hydroxy-oxindole **15a** in good yield. These conditions were applied for the preparation of a small set of oxindole derivatives (Scheme 12, B). This cyclization which has no precedent with simple amide^[25] is particularly noteworthy as under these conditions, the amide should exhibit a low nucleophilic behavior due to its expected protonation by triflic acid used in large excess.

A) Rearrangement to hydroxybenzimidazoles



B) Aza-Nazarov cyclization of 5 and 11

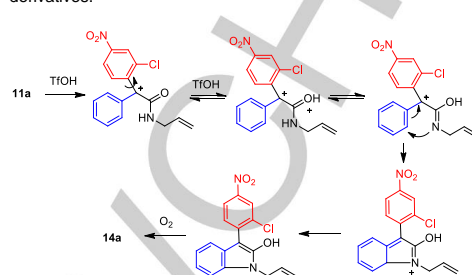


a) *p*-methoxybenzyl (PMB). b) NMR yields using 1,3,5-trimethoxybenzene as internal standard. c) **15a** was obtained in 62% isolated yield. d) isolated yields using 10 equiv. of triflic acid in CH₂Cl₂. e) prepared from **11d**. f) prepared from **11i**. g) prepared from **5p**.

Scheme 12.

Under the conditions of our cyclization, the tautomerization of the amide into its hydroxy-imidate isomer probably helps triggering the following aza-Nazarov cyclization. A final oxidative process is then observed in the presence of oxygen dissolved in the solvent (Scheme 13). This last oxidative step is very efficient in the

condition of the reaction, as we could not isolate any CH oxindole derivatives even trying to work in prior degassed solvent. In all the sequence, the nitroaryl moiety is twisted in order to lower its destabilizing interaction with the benzylic cation leading to a preference for the richer aryl moiety in the aza-Nazarov step as well non-productive Nazarov cyclization towards fluorene derivatives.



Scheme 13.

Conclusion

In conclusion, we have settled complex Phospha-Brook/Smiles cascades from 2 and 4-nitrophenols leading to families of bisarylacetamides, hydroxy-benzimidazoles and oxindoles. Of particular significance, this study gathers:

- Complex cascades involving Phospha-Brook shifts embedded with Smiles rearrangements.
- New data on 1,3-Truce-Smiles rearrangement, a shift involving 4-membered ring intermediates with very few precedents in the literature.
- A very original conversion of 2-nitrophenols into benzimidazoles with an unprecedented σ - π metathesis of a nitroso-ketoamides intermediate.
- DFT studies highlighting the most challenging reaction mechanisms.
- Increased synthetic significance thanks to multiple entries for starting materials (Passerini-Smiles as well as Pudovik reactions).
- A new triflic acid triggered aza-Nazarov cyclization of amides towards oxindoles, a reaction only reported for more nucleophilic *N*-alkoxy-amides.

Main Text Paragraph.

((Note: Please place comprehensive details in the Supporting Information.))

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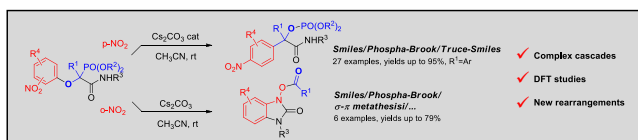
Keywords: Smiles rearrangement • Truce-Smiles rearrangement • Passerini reaction • Phospha-Brook rearrangement •

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A Smiles festival: Passerini-Smiles reactions of α -ketophosphonates with 2 and 4-nitrophenols lead the way towards complex cascades tuned by further Smiles and Truce-Smiles rearrangements

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