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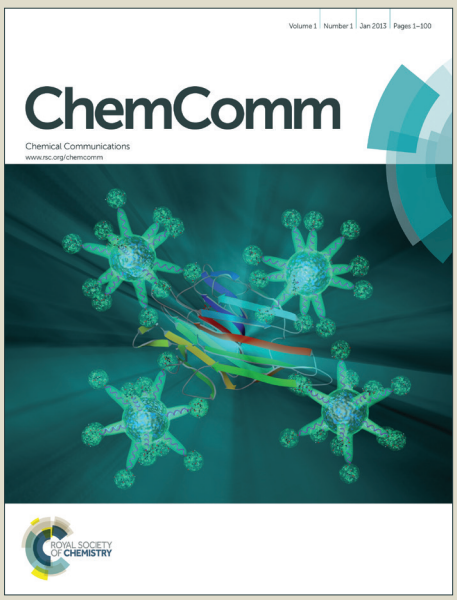

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Double Smiles rearrangement of Passerini adducts towards benzoxazinones.

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E. Martinand-Lurin,[b,c] A. Dos Santos,[a] L. El Kaim,*[a] L. Grimaud*[b] and P. Retailleau[c]

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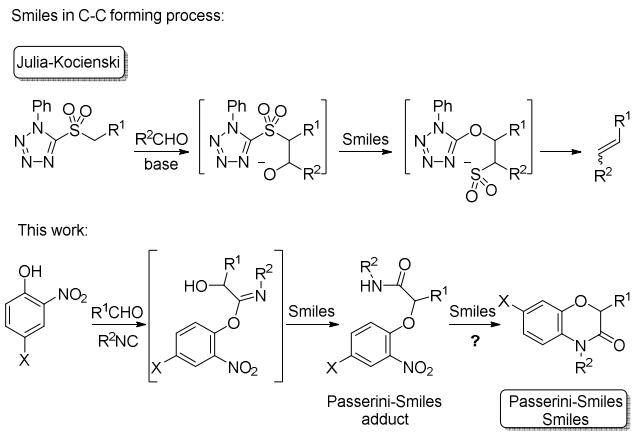
A new straightforward access to benzoxazinones based on a three-component coupling is presented here. The mechanism of the whole process involves a double aryl transfer as clearly underlined by the X-ray diffraction analysis of the products.

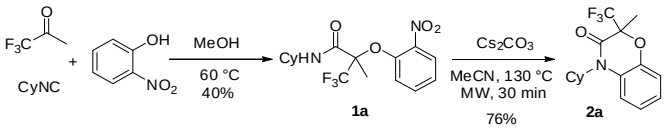
Smiles rearrangements consist in the transfer of an aromatic ring from one heteroatom to another one located in the same chain. Thoroughly studied by Samuel Smiles in 1930s,[1] the synthetic interest for these rearrangements[2] was recently rekindled by their integration in complex synthetic cascades. Among these, one of the most impressive use of Smiles rearrangements in carbon-carbon forming reaction appeared as a key step in the Julia-Kocienski olefin synthesis (Scheme 1).[3,4] A few years ago, we reported that Smiles rearrangements could trigger new isocyanide-based multicomponent reactions involving hydroxyaromatics such as nitrophenols or hydroxypyridines (Ugi-Smiles[5] and Passerini-Smiles[6] couplings). Considering the structures of Passerini-Smiles adducts and knowing that Smiles rearrangements usually favor *N*-aryl derivatives over *O*-aryl ones, we envisioned that these adducts could undergo a second Smiles rearrangement towards *N*-arylamides (Scheme 1).

If such transformation could be performed in a one-pot procedure from the starting Passerini components, it would represent the first carbon-carbon bond forming process featuring two Smiles rearrangements as key steps. Herein, we wish to present our progress towards this Passerini-Smiles-Smiles sequence and report on a new 1,4-benzoxazinones synthesis together with improved conditions for the three-component coupling.



Scheme 1 Smiles rearrangements in C-C bond forming reactions.

The Passerini-Smiles reaction of 1,1,1-trifluoroacetone was chosen to demonstrate the feasibility of the cascade. Though the formation of such adducts is usually less efficient with ketones than aldehydes, the following formation of the Smiles spiro intermediate is expected to be favored by a Thorpe-Ingold effect. Smiles rearrangement of amides is usually performed in polar solvent under basic conditions. When the adduct **1a** was treated with potassium or cesium carbonate in acetonitrile under reflux conditions no transformation could be observed. However, we were delighted to observe a clean formation of benzoxazinone **2a** under microwave irradiations at 130 °C (Scheme 2).

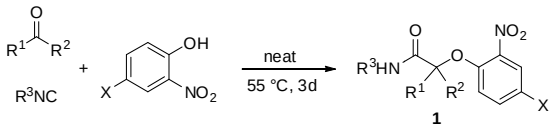


Scheme 2 First trial of Passerini-Smiles-Smiles.

Before addressing the mechanism of this transformation by a proper substitution of the aromatic moiety, we decided to spend more time on the first Passerini step. Our initial report on the Passerini-Smiles reaction proposes methanol as solvent heating at 40 to 60 °C under concentrated condition (1 M). Under prolonged heating, methanol slowly evaporates and a stable concentration is difficult to maintain. As a consequence, we found that yields were difficult to reproduce with both aldehydes and ketones showing a strong dependence of the reaction vessel and scale.

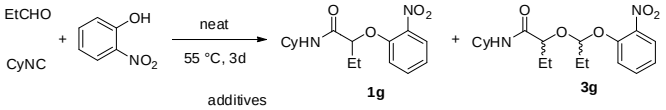
Performing the Passerini-Smiles reaction in neat conditions as recently reported for Passerini coupling[7] significantly improved the procedure for ketones. As classically observed in Passerini-type reactions, they are more reluctant to react than aldehydes and required one to three days of heating for completion. Simple ketones such as pentan-2-one or cyclohexanone do not react (Entries 2-3, Table 1) but strained ones (entries 4-6, Table 1) or ketones bearing electron-withdrawing groups (entries 1 and 7-8, Table 1) are activated enough to be coupled under these conditions. The reaction is efficient even with substituted 2-nitrophenols (entries 4, 6 and 8, Table 1).

Table 1 Scope of Passerini Smiles couplings with ketones.



Entry	R^1	R^2	R^3NC	X	Product (Yield)
1	CF_3	CH_3	CyNC	H	**1a** (78%)
2	Et	Et	CyNC	H	-
3			CyNC	H	-
4			CyNC	Cl	**1b** (50%)
5				H	**1c** (63%)
6				Br	**1d** (58%)
7	CH_2OCH_3	CH_3	CyNC	H	**1e** (65%)
8	CH_2OCH_3	CH_3		Cl	**1f** (59%)

However, no improvement was observed with aldehydes under neat conditions. Indeed, when cyclohexylisocyanide and propionaldehyde were heated with 2-nitrophenol, an important amount of acetal **3g** was obtained as side-product with still unsatisfactory overall yields (Scheme 3). In order to improve the 3-CC with aldehydes, various additives were tested following Mironov study on the accelerating effect of 4-nitrothiophenol in Passerini couplings.[8] No substantial difference was observed with thiophenol but a stoichiometric amount of N,N-dimethylpiperazine afforded 57% of compound **1g** along with 5% of acetal **3g**. *N,N*-Diisopropylethylamine did not improve the coupling but N-Methylpyrrolidine slightly increased the yields. Finally, DABCO gave to best results as no traces of acetal could be detected in these conditions (Scheme 3).



additives	1g	3g
none	34%	10%
4-nitrothiophenol (5 mol%)	32%	9%
i-Pr_2NEt (1 equiv.)	34%	8%
N-methylpyrrolidine (1 equiv.)	66%	2%
DABCO (0.5 equiv.)	58%	4%
DABCO (1 equiv.)	65%	0%
N,N-dimethylpiperazine (1 equiv.)	54%	2%
tetramethylenediamine (1 equiv.)	60%	4%
DBU (1 equiv.)	9%	0%

Scheme 3 Passerini-Smiles couplings of aldehydes with additives.

To gain further insight in the role of DABCO and *N,N*-dimethylpiperazine, a kinetic study was performed for the coupling of *i*-butyraldehyde with 2-nitrophenol and cyclohexylisocyanide. The progress of the reaction was followed by NMR and the results shown in Figure 1. In both cases, yields and reaction times are dramatically impacted by the presence of the tertiary amine. Indeed, after 3 hours, the reactions performed with additives did not evolve notably and the desired adduct **1j** was isolated in 74% and 65% with DABCO and *N,N*-dimethylpiperazine respectively, instead of 35% without additive. In order to improve even more the conversion rate, the reaction was performed using two equivalents of aldehyde, affording with one equivalent of DABCO **1j** in 91% yields after 12 h. The effect of the added amine on acetal formation is best explained by a possible storage of the aldehyde as an intermediate hemiaminal, disminishing thus the probability for a second molecule to interact with the three other partners. The amine may act as a relay in the required proton transfers as well, which can explain the observed kinetic enhancement. It is worth noting that the addition of DABCO with ketones has a detrimental effect on yields. In this case, acetal formation is not operative and base triggered self-condensation of the ketones could constitute a competitive pathway.

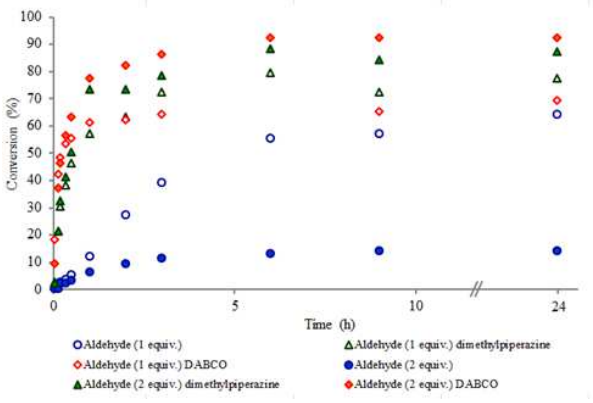
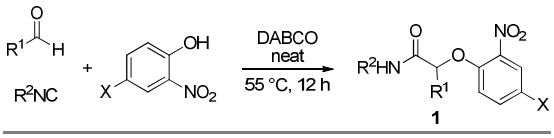


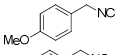
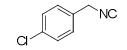
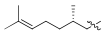
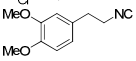
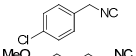
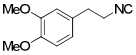
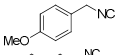
Figure 1 Kinetic studies and additives.

A set of aldehydes, nitrophenols and isocyanides were treated under these conditions and the reactions stopped after 12 hours. The reaction is efficient for various aliphatic aldehydes. Substituents on the phenol do not affect the process and the reaction is still efficient with both electron-withdrawing (entries 5-6 and 8-13, Table 2) and -donating groups (entries 7 and 14, Table 2).

Table 2 Scope of Passerini-Smiles couplings with aldehydes.

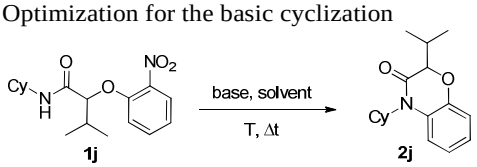


1

Entry	R^1	R^2NC	X	Product (Yield)
1	Et	CyNC	H	**1g**(88%)
2	*t*-Bu	CyNC	H	**1h**(85%)
3	CH_2CH_2Ph	CyNC	H	**1i** (85%)
4	*i*-Pr	CyNC	H	**1j** (91%)
5	Et	*t*-BuNC	Cl	**1k** (79%)
6	Et		CN	**1l** (61%)
7	*i*-Bu		Me	**1m** (72%)
8			CF_3	**1n** (82%)
9	*i*-Pr	*t*-BuNC	Cl	**1o** (68%)
10	*t*-Bu		Cl	**1p** (86%)
11	*i*-Pr		Br	**1q** (96%)
12	*t*-Bu		Br	**1r** (78%)
13			Me	**1s** (83%)
14	*t*-Bu		MeO	**1t** (78%)

The second Smiles rearrangement was next investigated. When the conditions settled for **1a** were tested with **1j**, no cyclization was observed. The reaction was thus optimized to find suitable conditions for Passerini-Smiles adducts formed from both aldehydes and ketones (Table 3).

Table 3. Optimization for the basic cyclization



1j 2j

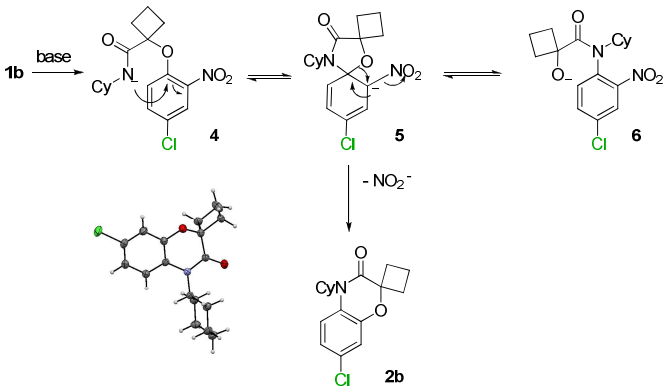
Entry	Base (equiv.)	Solvent	T (°C)	Rxn Time	Yield (SM)
1	Cs_2CO_3 (1)	MeCN	130 (μW)	30 min	8 (89)
	Cs_2CO_3 (1)	DMF	100	3h	0 (100)
3	DBU (1.5)	DMF	100	3h	0 (100)
4	NaH (2)	DMF	100	3h	54 (30)
5	KH (1.5)	DMF	100	3h	69 (10)
6	*t*-BuOK (1.5)	MeCN	75	2h	28
7	*t*-BuOK (1)	DMF	100	2h	79 (17)
8	*t*-BuOK (1.5)	DMF	100	2h	76 (0)
9	*t*-BuOK (1.5)	DMF[a]	100	1h	89 (0)
10	*t*-BuOK (1.5 or 2)	DMF	120	2h	83 (0)
11	Cs_2CO_3(1)+NaH (1.2)	THF	100	3h	75 (25)
12	Cs_2CO_3(1)+NaH (1.2)	DMF	100	3h	58 (13)
13	Cs_2CO_3 (1)+NaH (1.2)	DMF	120	3h	81 (3)

[a]The concentration of the reaction mixture was 0.2M instead of 0.4M.

Whereas combination of cesium carbonate with NaH or DBU in acetonitrile or THF proved unsatisfactory, stronger bases in more polar solvent gave good conversions. Best conditions were obtained either with a NaH/Cs_2CO_3 combination or with potassium *tert*-butoxide in DMF (entry 1, Table 3). In the former case, a more reactive cesium amide intermediate is probably formed along the process.

For simplicity, potassium *tert*-butoxide was selected as the base in DMF as solvent, and a set of Passerini-Smiles adducts **1** were submitted to these conditions (Table 4).

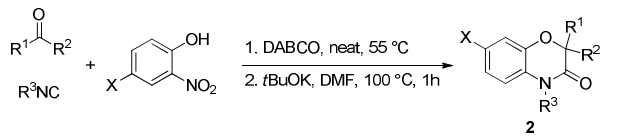
The cyclization of adduct **1b** shed some light on the mechanism of the cyclization. X-ray analyses of **2b** demonstrate a *para*-substitution pattern between the chloro and the nitrogen atoms of the aromatic core rejecting a direct substitution of the nitro group by the amide anion. The mechanism most probably involves the formation of the Meisenheimer intermediate **5** which settles a Smiles rearrangement between the amide anion **4** and the alcoholate **6**.[2] Hydrolysis of the alcohol is not observed in this case as a displacement of the nitro by the oxygen atom of the spiro in **5** shifts the equilibrium towards benzoxazinone **2b**. This analysis is confirmed by few nitro group displacements under Smiles transfer conditions[9] as well as several theoretical studies concerning SNAr reactions coupled with these rearrangements.[10]



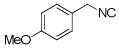
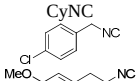
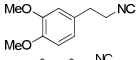
Scheme 4 Mechanism of the cyclization.

Finally, the whole process was attempted according to a one-pot procedure. After the Passerini-Smiles step performed in neat conditions, DMF was added together with potassium *tert*-butoxide and the mixture heated for one hour at 100 °C. Rewardingly, the DABCO introduced in the first step does not disturb the following cyclization and good yields were obtained for a set of aldehydes and ketones as shown in Table 4.

Table 5. One-pot procedure



2

Entry	R_1	R_2	R_3NC	X	Product (Yield)
1	CF_3	CH_3	CyNC	H	**2a** (71%)[a]
2				H	**2c** (61%)[a]
3	CH_2OCH_3	CH_3	CyNC	H	**2e** (48%)[a]
4	*i*-Pr	H	CyNC	H	**2j** (88%)
5	*t*-Bu	H		Cl	**2p** (89%)
6	*i*-Pr	H		Br	**2q** (65%)
7	*t*-Bu	H		OMe	**2t** (63%)

[a] DABCO was not added for reactions with ketones.

Conclusions

We have disclosed here a new isocyanide based multicomponent access towards benzoxazinones. It represents one of the most advanced and powerful use of Smiles rearrangement in synthesis displaying a cascade of two Smiles rearrangements coupled with a carbon-carbon bond formation. The nitro group plays a central role in the process triggering both Smiles before is elimination at the end of the sequence. Besides these mechanistic features, the one-pot formation of benzoxazinones from *o*-nitrophenol has a high interest in medicinal chemistry as these heterocycles display a wide array of biological activities.[11]

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Notes and references

[a]UMR 7652 (Ecole Polytechnique/ENSTA/CNRS), Laboratoire Chimie et Procédés, ENSTA-ParisTech, 828 Bd des maréchaux, 91120 Palaiseau, France. Tel: 0033181872020; E-mail: laurent.elkaim@ensta-paristech.fr.
[b]UPMC-ENS-CNRS-UMR 8640. Ecole Normale Supérieure-Département de chimie. 24 rue Lhomond, 75231 Paris cedex 05, France. E-mail :laurence.grimaud@ens.fr.
[c]UPR 2301 CNRS. Centre de Recherche de Gif-sur-Yvette, Institut de Chimie des Substances Naturelles. Avenue de la Terrasse, 91198 Gif-sur-Yvette,France.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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