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Preparation of 2*H*-1,4-Benzoxazin-2-one Derivatives under Heterogeneous Conditions *via* Domino Process

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Abstract: Carbonate on polymer is a valuable solid supported reagent (SSR) to promote, under eco-friendly conditions, the preparation of 2*H*-1,4-benzoxazin-2-one derivatives starting from β-nitroacrylates and aminophenols *via* a domino process.

Keywords: 2*H*-1,4-benzoxazin-2-ones; domino process; multi-step reaction; β-nitroacrylates; solid supported reagents

In an age when organic chemists have shown that even the most complex natural and unnatural products can be synthesized,[1] the emphasis of synthetic chemistry is shifting to how they can be assembled in a truly practical fashion.[2] A pressing challenge facing organic chemists, therefore, is to advance new processes that are not only efficient, selective, and high yielding but also environmentally friendly, especially having decreased solvent requirements.[3] The use of solid supported reagents (SSR) is undeniable a possible answer to increase the eco-sustainably of a process. In fact the use of a solid system consents to reduce the work-up to an easy filtration and evaporation of the solvent, avoiding aqueous layers and consequently the use and the formation of salts, which are the main causes to increase the *environmental factor* and the formation of the waste.[4] In addition, the reaction performed by SSR, can be monitored using straightforward techniques, such as GC- and HPLC-MS or by NMR spectroscopy, and finally an excess of reagents can be employed, in cases where needed, to drive the reaction to completion.[5]

Following our studies on the application of solid heterogeneous catalysis in combination with the chemistry of aliphatic nitro compounds,[6] we have found that commercially available carbonate on polymer support[7] promotes the reaction between β-nitroacrylates **1** and *o*-aminophenols **2** giving a direct synthesis of 2*H*-1,4-benzoxazin-2-one derivatives **6** (Scheme 1). β-Nitroacrylates are an emerging class of functionalized nitroalkenes that show high chemical versatility since they have been employed as strategic starting materials for the preparation of a variety of fine chemicals[8] and natural products.[9]

Benzoxazines constitute a class of compounds of important biological interest,[10] in particular, 1,4-benzoxazin-2-one structures, usually synthesized by the reaction between *o*-aminophenols with α-keto esters[11–13] or alkyl propriolates,[14] are of great interest due to both their photochemical activity[11,15] and their presence in many important products such as cephalandole alkaloids,[16] analogues of squamocin,[17] drugs (such as psoralen plus UVA).[13]

A plausible mechanism of our reaction consists in a domino process in which four different transformations are involved: (i) hetero-Michael addition of the amine functionality to nitroolefins giving the intermediates **3**, (ii) intramolecular transesterification with formation of **4**, (iii) elimination of a molecule of nitrous acid affording the intermediates **5**, and (iv) [1,3]-proton shift with the formation of target products **6**, as previously reported in the literature.[14]

With the view to optimizing the process, we investigated the reaction using stoichiometric amounts of β-nitroacrylate **1a** and 2-aminophenol **2a**, in ethyl acetate as eco-friendly solvent,[18] under different conditions. Thus, as reported in Table 1, the best result was obtained in the presence of an equimolar amount of carbonate on polymer, at 55 °C for 5.5 h (entry b), however, a comparable result was also obtained at 35 °C after 24 h (entry a).

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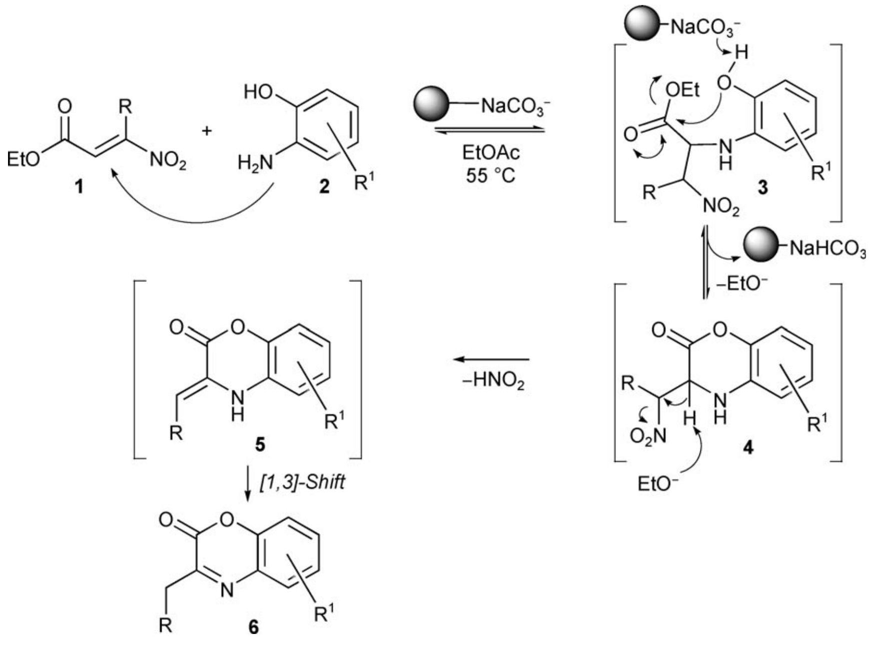
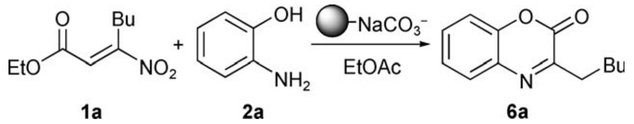


Scheme 1.

Table 1.

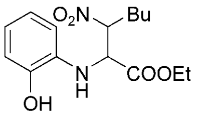


Entry	Carbonate on polymer (mol%)	T [°C]	Yield [%][a] of **6a**	t [h]
a	100	35	72	24
b	100	55	77	5.5
c	50	55	23	24
d	200	55	51	5.5

[a] Yield of pure product.

In order to verify the importance of the promoter, we examined the reaction both in the absence and under different amounts of SSR. The synthesis in the absence of carbonate on polymer, after one day, provided both the starting materials and the adduct **7** due to the hetero-Michael addition of the amine to β-nitroacrylate (Figure 1).

On the other hand, the presence of 50 mol% of carbonate on polymer gave, after one day, **6a** in poor yield (23%) (entry c), while the presence of 200 mol% of the promoter afforded **6a** in 51% yield (entry d).



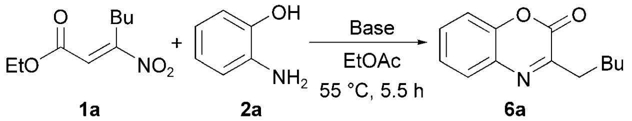
7

Figure 1.

Then, the efficiency of the carbonate on polymer support was compared with other standard promoters, and the sample reaction was investigated in the presence of a variety of other bases. However, as showed in Table 2, the best yield was still obtained in the presence of carbonate on polymer.

Finally, with the purpose to enlarge the potential of our procedure, we extended the methodology to a variety of β-nitroacrylates and *o*-aminophenols. As reported in Table 3, all the products were isolated in satisfactory to excellent overall yields (45–90%). In addition, the mild reaction conditions needed allow

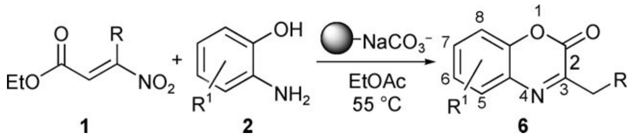
Table 2.



Entry	Base	Yield [%][a] of **6a**
a	Carbonate on polymer support[b]	77
b	K_2CO_3[b]	51
c	Amberlyst A-21[c]	43
d	TBD[b]	40
e	Basic alumina[c]	13

[a] Yield of pure product.
[b] 1 equivalent of base was used.
[c] 1 g of base for each mmol of **2a** was used.

Table 3.



Entry	R	R^1	Yield [%][a] of **6**	*t* [h]
a	Bu	H	77	5.5
b	$Me(CH_2)_4$	H	85	5.5
c	$NC(CH_2)_4$	H	65	2.5
d	$Ph(CH_2)_2$	H	82	5.5
e	$Me(CH_2)_6$	H	75	7
f	Me	H	51	5.5
g	$(Me)_2CH(CH_2)_2$	7-Me	75	5
h	$MeOCO(CH_2)_4$	7-Me	68	6
i	Me	7-Me	63	5.5
j	$CH_2{=}CH(CH_2)_8$	7-Me	66	7
k	$Me(CH_2)_4$	7-Me	90	5.5
l	Me	6-Cl	45	5.5
m	$(Me)_2CH(CH_2)_2$	6-Cl	55	6

[a] Yield of pure products.

the survival of different functionalities such as ester, cyano, aromatic groups and C=C double bonds.

Compared with other reported procedures,[11–14] our approach shows higher eco-sustainability thanks to the use of the solid supported promoter. In fact the use of solvents is minimized, reducing the classical tedious work-up to an easy filtration and evaporation. In addition, the catalyst can be recycled (**1a** and **2a** to **6a** was chosen as model reaction) with similar yields (reaction 77%; 1st recycle 75%, 2nd recycle 75%, 3rd recycle 74%) after its reactivation, following the reported procedure.[19]

Moreover, by our method a large variety of alkyl groups (R) can be easily introduced, just by the right choice of the appropriate nitroalkane during the preparation[8a] of the β-nitroacrylates.

In conclusion, we have found a new, chemoselective, eco-friendly synthetic process for the preparation of a valuable class of bicyclic compounds such as 2*H*-1,4-benzoxazin-2-ones, in which four different transformations can be performed one-flask, different functionalities can be preserved, just a small amount of eco-friendly solvent (EtOAc) is needed, and good overall yields are obtained.

Experimental Section

Typical Procedure for the Synthesis of 2*H*-1,4-Benzoxazin-2-ones

To a stirred solution of the β-nitroacrylate **1** (1 mmol) in EtOAc (2 mL), the appropriatee aminophenol **2** (1 mmol) and the carbonate on polymer (1 mmol, 286 mg) were added. The resulting reaction mixture was heated at 55 °C and stirred for the required time (the reaction progress was monitored by withdrawing aliquots, which were analyzed by TLC, see Table 2), then the catalyst was filtered off, washed with EtOAc, the filtrate was concentrate under vacuum to give the crude products **6a–m**, which were purified by flash chromatography column (hexane-ethyl acetate).

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