Efficient two-step sequence for the synthesis of 2,5-disubstituted furan derivatives from functionalized nitroalkanes: successive Amberlyst A21- and Amberlyst 15-catalyzed processes†

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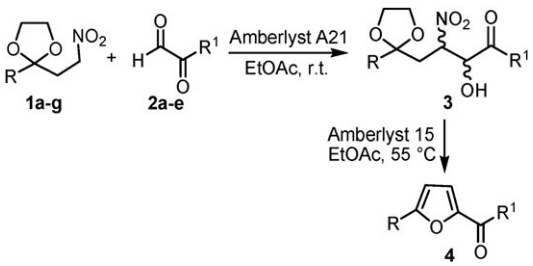
The nitroaldol reaction of ketal-functionalized nitroalkanes with α-oxoaldehydes, promoted by Amberlyst A21, followed by acidic treatment (Amberlyst 15) of the obtained nitroalkanol, leads to the formation of 2,5-disubstituted furans in good yields. The procedure was successfully applied to the total synthesis of 1-benzyl-3-(5′-hydroxymethyl-2′-furyl)-indazole (YC-1), an important pharmaceutical target.

Functionalized furans are found as key structural moieties in many bioactive natural products and important pharmaceuticals,[1] moreover, they are also useful intermediates in organic synthesis by virtue of their specific chemistry and latent functionality.[2] Although these properties have motivated the development of several methods for the synthesis of furans,[3] there is still a great need for new furan derivatives and *de novo* routes for their preparation. Thus, the availability of uncomplicated synthetic procedures that enable the preparation of polysubstituted furans is an important task for organic and medicinal chemists. These facts, combined with our previous experience in the synthesis of heterocycles from aliphatic nitrocompounds,[4] have led us to explore a new approach for the synthesis of functionalized 2,5-substituted furans.

In recent years, there has been a growing interest in the use of nitroalkanes as key starting chemicals in the synthesis of various heterocycles.[5] Thus, as a development of our research, herein we present an innovative, mild and efficient method, for the synthesis of a series of 2,5-disubstituted furans **4** starting from functionalized nitroalkanes of type **1**.[6] As reported in Scheme 1, the synthetic strategy was initially planned as two independent steps, starting from the nitroaldol (Henry) reaction of **1** with the aldehyde **2**,[7] under basic conditions, followed by acid treatment of the obtained β-nitroalcohol **3**.

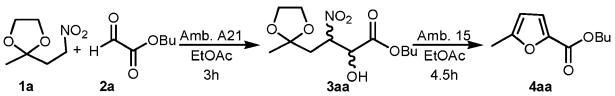
Based on the high reactivity that nitro compounds showed recently under solid heterogeneous catalysis,[8] and with the scope to optimize the process, we investigated both the steps under different amounts of Amberlyst A21 (anionic macromolecular ion-exchange resin) and Amberlyst 15 (cationic macromolecular ion-exchange resin), respectively. We have chosen, as a model, the reaction of an equimolar ratio of **1a** (R = Me) with **2a** (R^1 = OBu) in the minimum amount of ethyl acetate, as an eco-friendly solvent.[9] As reported in Table 1, the best result of the first step was obtained using 0.5 g of Amberlyst A21 per mmol of substrate at room temperature, while the best performance of the second step, needs 0.7 g of Amberlyst 15 per mmol of substrate, at 55 °C.



Scheme 1 General pathway to the synthesis of furan derivatives.

Because both the steps gave good results under heterogeneous conditions, we modified our initial procedure in order to combine the two reaction steps and with the aim to produce directly, the target compound **4aa**, avoiding any isolation and purification of the intermediate **3aa** and increasing the eco-sustainability of the process.[10] The new revised procedure, consists of the nitroaldol reaction of **1a** with **2a** in ethyl acetate and at room temperature, promoted by Amberlyst A21, followed by filtration of the catalyst and successive addition of Amberlyst 15 to the percolate, containing the crude nitroalkanol **3aa**, and heating at 55 °C for the appropriate length of time (4–6 h). Thus, the direct formation of the furans **4aa** takes place in good overall yield (78%).

Table 1 Screening of different amounts of the two promoters



g of Amberlyst A21 per mmol of **1a**	Yield (%)[a] of **3aa**
0.3	73
0.5	81
0.7	80
g of Amberlyst A15 per mmol of 3aa	**Yield (%)[a] of 4aa starting from 3aa (temperature °C)**
0.5	Traces (rt)
0.5	72 (55)
0.7	81 (55)
0.9	80 (55)

[a] Yield of pure isolated product.

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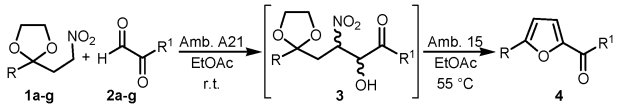
Table 2 Preparation by two-step route of the furan derivatives **4**



R	1	R^1	2	Reaction time of **3**/h	Reaction time of **4**/h	Overall yield (%)[a] of **4**
Me	**a**	OBu	**a**	**3aa** (3)	**4aa** (4.5)	78
Me	**a**	Ph[b]	**b**	**3ab** (7)	**4ab** (4.5)	65
n-C_5H_{11}	**b**	OBu	**a**	**3ba** (3)	**4ba** (4.5)	61
Ph	**c**	OEt[c]	**c**	**3cc** (3)	**4cc** (4)	80
p-PhC_6H_4	**d**	OEt[c]	**c**	**3dc** (3)	**4dc** (4.5)	60
Et	**e**	p-MeC_6H_4	**d**	**3ed** (4)	**4ed** (4.5)	56
Et	**e**	OBn	**e**	**3ee** (3)	**4ee** (4)	69
$Ph(CH_2)_2$	**f**	OEt[c]	**c**	**3fc** (8)	**4fc** (4.5)	84
$Ph(CH_2)_2$	**f**	Ph[b]	**b**	**3fd** (7)	**4fd** (4.5)	61
2-Naphthyl	**g**	Ph[b]	**b**	**3gb** (6)	**4gb** (6)	68

[a] Yield of pure isolated product. [b] Phenylglyoxal monohydrate was used. [c] Ethyl glyoxalate solution 50% in toluene was used.

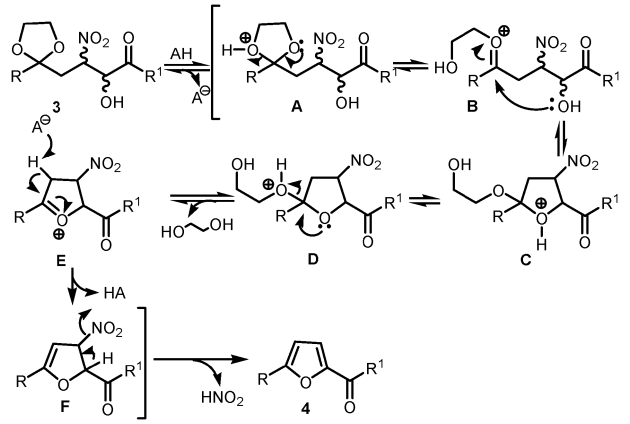
In order to verify the generality of our procedure, we extended the methodology to a variety of nitroalkanes **1** and aldehydes **2**. As reported in Table 2, all the products were isolated in good overall yields (56–84%), independently from the nature of both (i) the alkyl or aryl groups (R) in the nitroalkanes **1** and (ii) the α-oxoaldehyde derivatives **2**.

A plausible mechanism for the one-pot conversion of the nitroalcohols **3** into the furans **4** is reported in Scheme 2, in which the formed nitroalkanol **3** is protonated at the oxygen with the formation of the intermediate **A**. The latter, leads to the opening of 1,3-dioxolane ring with the formation of **B**, which proceeds to the hetero-cyclization by the attack of the hydroxyl group to the oxonium cation, affording the intermediate **C**. Then, the process undergoes an acid–base equilibrium (**D**) followed by the elimination of a mole of ethylene glycol, with the formation of the structure **E** which is converted, after deprotonation (**F**) and elimination of nitrous acid, into the target furan system **4**. Thus, by the appropriate choice of the nitroalkane **1** it is possible to introduce the needed alkyl (or aryl) group at 5-position of the target furan **4**.

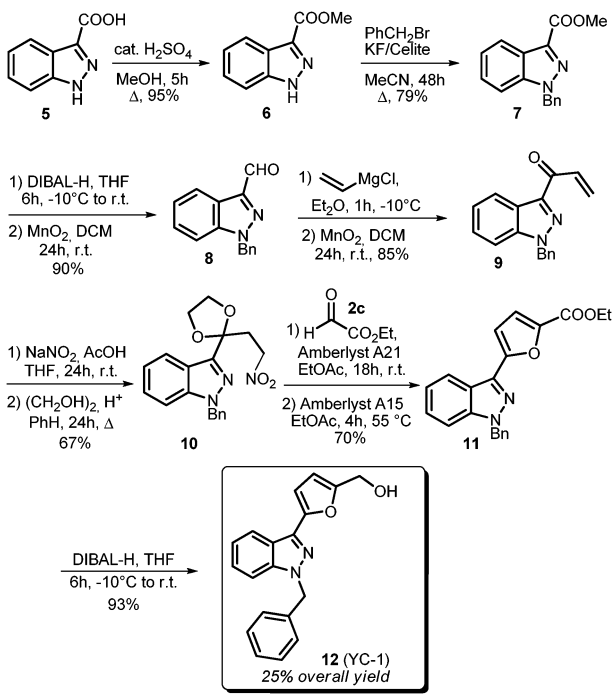
Moreover, it is important to note the key role of the nitro functionality that firstly acts as good electron-withdrawing group, allowing the generation of a new C,C bond (**1** + **2** to **3**), then as good leaving group favoring the generation of a new C,C double bond (**F** to **4**) by elimination of nitrous acid.

As a practical application of our procedure we report here the total synthesis of 1-benzyl-3-(5′-hydroxymethyl-2′-furyl)-indazole (YC-1) (Scheme 3), a very important pharmaceutical target that exhibits significant inhibitory effects against thrombin-, AA-, collagen-, and PAF-induced platelet aggregation.[11]

The synthesis starts from the commercially available indazole-3-carboxylic acid **5**, which was converted into the corresponding methyl ester **6**, by methanol and in the presence of sulfuric acid.[12] Then, **6** was benzylated by CsF-Celite, with MeCN as solvent and under reflux for 48 hours, affording the derivative **7**.[13] The latter was initially reduced, by DIBAL-H, to the corresponding primary alcohol, which was then



Scheme 2 Proposed reaction mechanism for the formation of furan derivatives **4**.



Scheme 3 Synthetic pathway of biologically active compound **12** (YC-1).

submitted to oxidation, by activated MnO_2 in DCM, affording the aldehyde **8**.[12] The compound **8**, was then alkylated with vinylmagnesium chloride in diethyl ether at −10 °C, affording the corresponding allylic alcohol, which was directly converted into the α,β-unsaturated ketone **9**, under MnO_2 and DCM oxidation. Then, the enone **9** was nitrated using $NaNO_2$, in the presence of AcOH and in THF, and the formed crude β-nitro ketone was protected by ethylene glycol, under refluxing benzene and using the Dean Stark apparatus.[6] Finally, **10** was reacted with ethyl glyoxalate following our procedure (Amberlyst A21 and Amberlyst 15) affording the furan derivative **11**, which was reduced by DIBAL-H into the target product **12** (YC-1) and in 25% overall yield.

Although, the overall yield of our approach is comparable to the main already reported procedures,[14] differently to them, our approach involves for the first time, to the best of our knowledge, the formation of furan ring during the synthetic process. This peculiarity could offer an easy access to a library of analogs of the compound **11**, having similar activity to the target **12**,[14d,15] by the appropriate selection of the aldehyde **2**.

In conclusion, our method represents an unprecedented, simple and regiodefined synthesis of functionalized 2,5-di-substituted furan derivatives, avoiding any isolation and purification of the intermediates. In addition, the good overall yields obtained and the practical applicability of our procedure have been successfully engaged for the total synthesis of a very important pharmaceutical target such as 1-benzyl-3-(5′-hydroxymethyl-2′-furyl)-indazole (YC-1).

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