Study on the Influence of a Sustainable Medium for the Design of Multistep Processes: Three-Component Synthesis of 2-Nitroamines

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Abstract: An environmentally benign method was developed for the three-component, one-pot synthesis of 2-nitroamines by heating a solution of an aldehyde, an aromatic amine, and a nitroalkane in 20% water–methanol at 60 °C for five hours in the absence of a catalyst.

Key words: coupling, Mannich bases, multicomponent reactions, Schiff bases, solvent effects

Multicomponent reactions (MCRs) are powerful tools in organic synthesis because, by changing the reaction conditions or by adding further reagents, libraries of products can be prepared through formation of several bonds in a single operation without isolation of intermediates.¹ In addition to their usefulness in synthetic chemistry, MCRs provide more environmentally benign methods for syntheses of complex molecules, as they involve simple operations with minimal production of waste materials and minimal energy consumption.² The eco-efficiency of a given MCR can be further enhanced by performing the reaction without a solvent or in a green solvent, such as water or an alcohol, and in the absence of any added catalyst.³

Usually the steps of an MCR involve well-known reactions, the novelty of the process lying in the sequential combination of various reactions under the same (preferably green) experimental conditions to give the final product in a one-pot process, saving time, energy, and raw materials, with consequential economic and environmental benefits.

In earlier studies, we reported that multistep and multicomponent reactions involving a dehydration step (the production of an imine from a carbonyl compound and an amine) can be performed efficiently in water in the presence of a solid catalyst or without a catalyst.⁴ We surmised that this reaction might provide an intriguing first step for a three-component reaction. According to the general rules of the MCR strategy,¹ the first step must proceed

SYNLETT 2013, 24, 2596–2600 Advanced online publication: 16.10.2013 DOI: 10.1055/s-0033-1339898; Art ID: ST-2013-D0688-L © Georg Thieme Verlag Stuttgart · New York rapidly to produce an intermediate that subsequently undergoes a second reaction to afford a final product.

On the basis of these results, and taking into account the well-documented possibility that synthetic processes involving aliphatic nitro compounds can be performed in aqueous media,⁵ we planned to investigate the synthesis of *N*-(2-nitro-1-phenylethyl)aniline (**5aaa**) by a three-component reaction of benzaldehyde (**1a**), aniline (**2a**), and nitromethane (**4a**) in water (Scheme 1).



Scheme 1 Three-component synthesis of *N*-(2-nitro-1-phenyle-thyl)aniline (5aaa)

We assumed that a fast initial condensation between benzaldehyde (1a) and aniline (2a) should give the intermediate imine 3aa, which would then undergo addition of nitromethane (4a) to give the nitro amine 5aaa by a typical nitro-Mannich process⁶ in the presence of a convenient catalyst or, better still, without an additional promoter.

The addition of nitroalkanes to imines to give 2-nitro amines can be achieved by using several promoters, such as a Brönsted acid,⁷ a stoichiometric amount of a Lewis acid,⁸ or the nitrogen-containing superbase 1,1,3,3-tetramethylguanidine.^{6d} An elegant three-component synthesis under solvent-free conditions catalyzed by 4-(imidazolium-1-yl)butane sulfonate has also recently been reported.⁹ Moreover, in recent decades a great deal of attention has been devoted to the development of protocols for performing enantioselective aza-Henry reactions.¹⁰ Initially, to facilitate analysis of the progress of the synthetic process, we disconnected the two steps of the threecomponent reaction. The first goal was to synthesize the intermediate imine **3aa** in water under mild conditions. To this end, we examined the model reaction shown in step (a) of Scheme 1, taking into account a procedure previously adopted by our research group,^{4a} and the results reported by Tanaka and co-workers.¹¹ As expected, imine **3aa** could be synthesized in high yield (92%) by treating benzaldehyde (**1a**; 1 mmol) with aniline (**2a**; 1 mmol) in water (5 mL) at 60 °C for five hours under biphasic conditions without a catalyst. It is worth underlining that this reaction represents an example of a high-yielding dehydration process that occurs in the presence of water.¹²

Our second goal was to perform the nitro-Mannich reaction between the intermediate imine **3aa** and nitromethane (**4a**) [Scheme 1, step (b)] to obtain the desired product **5aaa** with maximum yield and selectivity under conditions that were as similar as possible to those of the first step. The reaction between imine **3aa** (1 mmol) and nitromethane (**4a**; 10 mmol) was therefore performed in water and in a range of organic solvents (5 mL) without added catalyst. The most significant results are summarized in Table 1.

Within the range of concentrations explored, the medium had a marked effect on the efficiency of the process. The reaction gave the product **5aaa** in good yield and very high selectivity when performed in the absence of an add-ed catalyst in protic media such as water (68% yield, 96% selectivity) or methanol (77% yield, 95% selectivity) (Ta-ble 1, entries 1 and 2). The use of polar or nonpolar aprotic media, however, gave in only traces of product **5aaa** (entries 3–5), whereas solvent-free conditions gave product **5aaa** in 10% yield (entry 6). To the best of our knowledge, this is the first example of a nitro-Mannich reaction that is promoted by a protic solvent (water or methanol).

On the basis of these results, the optimal protocol for direct one-pot, three-component synthesis of nitro amine **5aaa** involves simply mixing benzaldehyde (**1a**; 1 mmol) with aniline (**2a**; 1 mmol) and nitromethane (**4a**; 10 mmol) in water (5 mL) at 60 °C with vigorous stirring. Product **5aaa** was obtained in 92% yield and 95% selectivity after 20 hours (Figure 1).



Figure 1 Yield and selectivity of product **5aaa** versus time. *Reagents and conditions*: benzaldehyde (1 mmol), aniline (1 mmol), nitromethane (10 mmol), H_2O (5 mL), 60 °C.

As can be seen from Figure 1, the reaction performed in water reaches a high yield ($\sim 60\%$) in a relatively short time (two hours). This is followed by a slow but continuous rise in yield to a maximum of 92% after 20 hours.

To check the possible activation effect of water¹³ and the contributions of hydrophobicity and micellar catalysis¹⁴ to this process, two series of reactions were performed with increasing amounts of water under biphasic conditions and with water-methanol mixtures of various molar ratios under homogeneous conditions. Figure 2 shows the effects of increasing the amount of water from 0 to 5 mL on the yield and selectivity of product **5aaa** in the model reaction.

The solvent-free reaction gave product **5aaa** in modest yield (10%), but addition of 0.5 mL of water to the reaction mixture produced a dramatic increase in reactivity, and product **5aaa** was obtained in 65% yield. The maximum yield of 72% was achieved when 1.5 mL of water was added and this value remained unchanged upon addition of larger amounts of water. A very high selectivity of about 95% was observed during all experiments.

Similar accelerating effects of water in various chemical reactions have previously been reported.^{13–15} The increase in reaction rate and selectivity is frequently ascribed to hydrophobic effects when insoluble organic reagents react in water.¹⁶ Some of these reactions have been termed

Entry	Medium	Conversion (%) of 3aa	Yield (%) of 5aaa	Selectivity (%) of 5aaa		
1	H ₂ O	71	68	96		
2	МеОН	81	77	95		
3	toluene	~4	~3	_		
4	2-methyltetrahydrofuran	~3	~3	_		
5	MeCN	~5	~4	_		
6	_	11	10	95		

Table 1The Nitro-Mannich Reaction of Benzaldimine 3aa and Nitromethane (4a) in Various Media or under Solvent-Free Conditions withoutan Added Catalyst

^a Reaction conditions: benzaldimine 3aa (1 mmol), MeNO₂ (4a; 10 mmol), medium (5 mL), 60 °C, 5 h.



Figure 2 Effects of addition of water on the yield and selectivity of product **5aaa**. *Reagents and conditions*: benzaldehyde (1 mmol), aniline (1 mmol), nitromethane (10 mmol), 60 °C, 5 h.

'on-water' reactions, because the reactants are located at a water–emulsion surface.¹⁷ However, it has been clearly stated by Breslow¹⁸ that, '... the simple observations of an increase of the reaction rate in water does not inevitably establish that a hydrophobic effect and a micellar cataly-sis are involved.'

To gain further information on the physicochemical parameters that control the process, we performed the model reaction in the presence of mixtures of water and methanol containing enough methanol to render the reactions homogeneous. For comparison, the reaction was performed in pure water and in pure methanol. The results are shown in Figure 3.



Figure 3 Effects of the water-methanol ratio on the yield and selectivity of product **5aaa**. *Reagents and conditions*: benzaldehyde (1 mmol), aniline (1 mmol), nitromethane (10 mmol), medium (1 mL), 60 °C, 5 h.

As already shown, good yields of product **5aaa** were obtained when the reaction was performed in pure methanol (77%) or pure water (68%). Interestingly, the addition of water to methanol, still under homogeneous conditions, resulted in an increase in the yield in comparison with that observed in pure methanol, and a maximal yield of 93% was obtained in 20% water–methanol. A similar trend was observed with nitroethane.

All the above results confirm that the model three-component reaction shown in Scheme 1, which proceeds very poorly under solvent-free conditions or in the presence of aprotic polar or apolar media, undergoes a dramatic rate acceleration when performed in the presence of water or, better, in a water-methanol mixture.¹⁹ The possible catalytic role of traces of both the amine and imine cannot be excluded; nevertheless, the above results provide evidence of a remarkable influence of the reaction medium, whose 'catalytic behavior' might be related to some peculiar properties, such as polarity/polarizability (water: 1.09; methanol: 0.60) or hydrogen-bond donor (water: 1.17; methanol: 0.98) or acceptor (water: 0.47; methanol: 0.66) abilities. The fact that the optimum yield was obtained with a particular water-methanol mixture might be due to a solubility effect or to an optimal combination of acid-base properties. Stabilization of the transition state by hydrogen bonding probably also has a comparable positive effect.^{13,20} Indeed, some preliminary studies have shown that neither the first step (production of imine **3aa**) nor the complete three-component reaction show any rate enhancement when performed in the presence of a saltingout agent such as lithium chloride, which is known to increase the hydrophobic effect.²¹

With the aim of increasing the sustainability of the process, we attempted to reduce the amount of the nitroalkane required. A good yield (87%) and excellent selectivity (96%) can be obtained by reducing the amount of nitromethane from 10 mmol to 5 mmol per mmol of benzalde-hyde and aniline; further decreases gave lower yields of product **5aaa**.

We then extended the procedure to various aromatic amines, aliphatic or aromatic aldehydes, and nitromethane (Table 2). The reaction proceeded efficiently with benzaldehyde (**1a**) or aryl aldehydes **1b**–e carrying either electron-withdrawing and electron-releasing groups (Table 2, entries 1–6). A lower reactivity was observed with the aliphatic aldehyde **1f** (entry 7). With aliphatic amines, the corresponding imines were obtained and no traces of the nitro amines were detected. Noticeably, the Henry byproduct, formed by attack of nitromethane on the aldehyde, was not observed; this selectivity was ascribed to the rate of the first step (imine formation) being higher than that of the Henry reaction.

Finally, we examined the effect of the length and branching of the alkyl moiety of the nitroalkane. A marked decrease in yield was observed in going from nitromethane (87% yield) to nitroethane (43%), 1-nitropropane (21%), and 2-nitropropane (traces). This behavior can be ascribed to a combination of steric hindrance and a decrease in the stability of the nitroalkane carbanion.²²

In summary, we have developed a new design and methodology for the three-component, one-pot synthesis of 2nitroamines. The process is efficiently performed by heating a solution of an aldehyde, an aromatic amine, and a nitroalkane at 60 °C for five hours without any added catalyst in 20% water-methanol. It should be underlined that, from the eco-sustainable standpoint, it would be preferable to use pure methanol to carry out the process. A series of experimental observations showed that the

Table 2	Preparation	of Various	Substituted	2-Nitroamines 5
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R ¹ CHC 1a–f	$D + \bigvee_{\substack{H^2 \\ H^2}} + 2a,b$	R ³ —N R ⁴ 4a–d	0 ₂ —	0% H ₂ C	9–MeOH ,5h	HN R ¹ R ³	NO_2 R^4 5
Entry	R ¹	R ²	R ³	R ⁴	Product	Yield (%)	Selectivity (%)
1	Ph	Н	Н	Н	5 aaa	87	96
2	$4\text{-}ClC_6H_4$	Н	Н	Н	5baa	88	97
3	$3\text{-}\mathrm{ClC}_6\mathrm{H}_4$	Н	Н	Н	5caa	87	98
4	$4-O_2NC_6H_4$	Н	Н	Н	5daa	78	97
5	$4-MeOC_6H_4$	Н	Н	Н	5eaa	83	98
6	Ph	OMe	Н	Н	5aba	90	97
7	Et	Н	Н	Н	5faa	64 ^a	91
8	Ph	Н	Me	Н	5aab	43 ^b	96
9	Ph	Н	Et	Н	5aac	21 ^b	97
10	Ph	Н	Me	Me	5aad	trace	-

^a Reaction carried out for 16 h.

^b Sum of diastereoisomers.

optimum yield and selectivity are obtained by using a 20% water-methanol mixture as a result of a synergistic combination of the solubility effect and optimal acid-base properties.

In a typical experiment, a solution of the appropriate aldehyde 1 (1 mmol), amine 2 (1 mmol), and nitroalkane 4 (5 mmol) in 20% H₂O–MeOH (1 mL) was heated in a closed reactor at 60 °C with stirring for five hours. The mixture was cooled to room temperature, water (5 mL) was added, and the mixture was extracted with ethyl acetate (2 × 5 mL). The combined extracts were dried (Na₂SO₄), filtered, and concentrated by distillation. The 2-nitroamines 5^{23} was isolated by column chromatography (silica gel, hexane–ethyl acetate).

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- (21) PhCHO (1a; 1 mmol) and PhNH₂ (2a; 1 mmol) were stirred in H₂O (5 mL) or 1 M aq LiCl (5 mL) at 60 °C for 10 min to give imine 3aa in 75 and 78% yield, respectively. In a second experiment, PhCHO (1a; 1 mmol), PhNH₂ (2a; 1 mmol), and MeNO₂ (4a; 10 mmol) were stirred in H₂O (5

mL) or 1 M aq LiCl (5 mL) at 60 $^\circ$ C for 30 min to give nitro amine **5aaa** in 37 and 39% yield, respectively.

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