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An expeditious, highly efficient, catalyst-free and solvent-free synthesis of nitroamines and nitrosulfides by Michael addition[†]

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A simple, atom economical, fast and highly efficient green protocol has been developed for the synthesis of nitroamines and nitrosulfides by the Michael addition of amines and thiols to nitroolefins by simple mixing or grinding. This catalyst-free and solvent-free green approach provided the addition products in quantitative yield within minutes at room temperature. This procedure does not require any water quenches, solvent separations and purification steps such as recrystallization and column chromatography.

Introduction

With the growing awareness in industry and academia for sustainable development, the international chemical community is under increasing pressure to alter current working practices and to find greener alternatives. As a result, green chemistry has been promoted worldwide by an increasing number of research groups because it provides transformations that are environmentally benign.^{1,2} A green protocol can be considered as a series of reductions such as costs, waste, energy use, materials consumption, risks and hazards, and non-renewables.³

The Michael reaction, being an atom economical reaction, fulfills the condition of incorporating all the constituents of the starting materials into the final product, required for a green protocol. The conjugate Michael addition of carbon nucleophiles to the electron deficient nitroalkenes is particularly interesting and challenging as it involves the generation of two chiral centres in a single step. The adducts, nitroamines and nitrosulfides, are versatile buildings blocks for the preparation of natural products and pharmacologically important targets and are used extensively in various organic reactions.⁴ Because of the presence of the nitro group, these products can be readily transformed into a variety of functionalities *e.g.*, they can be reduced to 1,2-diamines, which are an important structural motif in medicinal chemistry, or oxidized to α -amino acids by the Nef reaction.⁵

Nitroamines are typically synthesized by addition of nitro compounds to an azomethine function by an aza-Henry reaction mechanism⁶ (Scheme 1; Method-I). Several reports are available in the literature7-18 on direct addition of amines and thiols to nitroolefins for the synthesis of nitroamines and nitrosulfides (Scheme 1: Method-II). Owing to the importance of this reaction, these transformations were investigated under the catalytic activity of zirconium tetrakis(dodecylsulfate),⁷ samarium(III) triflate,8 tin(II) chloride,9 triethylamine in acetonitrile,10 L-proline in ionic liquid [bmim]PF₆,¹¹ copper(II) and nickel(II) chelates,¹² ammonium chloride,13 sodium acetate,14 TMAF.15 Catalyst free procedures in water are also known but they failed to carry out reactions with secondary aliphatic amines like morpholine.16 This method requires longer reaction times and involves work up followed by purification through recrystallization or column chromatography. The yields of the adducts with nitroolefins bearing groups such as chlorine are low and the transformations require longer reaction times.¹⁷ A catalyst-free and solvent-free procedure for the synthesis of nitrothiols from liquid samples of nitrostyrenes and thiols was also reported.¹⁸ However, this procedure requires stirring of the reaction mixture, column chromatographic purification of the products and it is not applicable for solid-solid reactants.



Scheme 1 Methods for the synthesis of nitroamines and nitrosulfides.

As part of our ongoing research work on the development of green approaches in organic synthesis, herein we report our results for a near absolute green protocol for the synthesis of nitroamines and nitrothiols by Michael addition of aromatic amines and aromatic thiols to nitroolefins under solvent-free and catalyst-free conditions. This method proceeds with simple mixing or grinding of stoichiometric amounts of the reactants to provide the pure addition products in quantitative yield.

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Results and discussion

Reaction between amines and nitroolefins

As a prelude to this objective, we carried out the reaction between liquid-solid reactants. Thus, equimolar amounts of aniline (1a) and nitrostyrene $(2a)^{19}$ were taken in a pre-weighed petri dish and mixed with spatula for two min and then the mixture was allowed to stand for five min. The progress of the reaction was monitored by thin layer chromatography. During this period, complete conversion from the reactants to the Michael adduct took place. After completion of the reaction, the weight of the petri dish along with the product was taken and found that the yield of the addition product 3a was quantitative. The purity of the product was good enough for spectroscopic analysis. Similarly, the mixing of 3,5dimethylaniline (1b) with nitrostyrene (2a) provided the Michael adduct 3b in quantitative yield. Subsequently, the reaction of solid reactants *p*-methoxyaniline (1c) and nitrostyrene (2a) was performed in a mortar and pestle by grinding the mixture for one minute at room temperature. Again in this case the yield of the pure product 3c was found to be quantitative (Scheme 2).



Scheme 2 Synthesis of nitroamines.

After a successful attempt with aromatic amines we further explored the reaction of nitrostyrene with morpholine, a secondary aliphatic amine. An exothermic reaction started immediately after mixing equimolar ratio of the reactants 1e and 2a with concomitant liquidification of the contents followed by solidification of the product 3d. A perfect solid product was obtained in excellent yield of 95%. However, when the reaction was carried out with slight excess (1.1 equiv) of morpholine, the Michael adduct 3d was obtained in quantitative yield. The adduct is quite stable and no back-conversion to the reactants was observed unlike the products of nitrostyrene with secondary amines obtained from the reaction in water.¹⁶

To expand the scope of the current green protocol, a series of reactions between variously substituted nitrostyrenes and selected anilines and morpholine were carried out. The products are shown in Table 1. All the reactions were performed under neat conditions without using any solvent or catalyst. In the course of our investigations, the solid-liquid combination reactions were carried out by simple mixing of stoichiometric molar ratios of both reactants with a spatula in a petri dish and allowing the contents to stand for five minutes if required. In the case of solid-solid combination reactions, the solid mixture was ground in mortar with pestle for one to three minutes and the contents were allowed to stand for five minutes if required to afford the pure products 3c, 3i, and 3j (Table 1, entries 3, 9 and 10). The reactions of morpholine with nitrostyrenes reached completion within one minute of mixing to afford the solid products.

It was also found that the nature of the substitution on the aromatic nucleus of the nitroolefin as well as on the aniline had great influence on the reaction. The electron withdrawing group on the arene moiety of the nitroolefin and electron donating group on aniline drive the reaction very fast. For instance, the reaction between *m*-nitro-nitrostyrene and *p*-anisidine reached completion within a minute. Similarly, the nitro-substituted β-nitrostyrenes reacted with morpholine within a minute. In contrast, the reaction between 4-hydroxynitrostyrene with aniline and the reaction between nitrostyrene with *p*-nitroaniline did not reach completion under the reaction conditions, and provided the corresponding adducts in 30% vield.

Reaction between aromatic thiols and nitroolefins

Inspired by above results we extended the grinding protocol for the synthesis of nitrosulfides in quantitative yields by using thiol as the nucleophile in place of aniline, with nitroolefins. A stoichiometric molar ratio of benzenethiol 4a and nitroolefin 2a were taken in a petri dish and mixed with a spatula for two minutes. The progress of the reaction was monitored by thin layer chromatography, and a new product was formed immediately. This reaction mixture was allowed to stand at room temperature for five minutes to reach completion. Thus the desired adduct 5a was obtained in quantitative vield.

To further explore this method, a series of nitrothiols 5br have been synthesized (Scheme 3) and results are summarized in Table 2. This method is applicable to various thiols i.e. benzenethiol, phenylmethanethiol, naphthalene-2thiol, 4-methoxybenzenethiol, 4-bromobenzenethiol and 4methylbenzenethiol with various nitroolefins. A wide variety of nitroolefins bearing groups such as 4-bromo, 4-chloro, 2-nitro and 3-nitro participated in the current protocol. In all these cases, the reaction proceeded smoothly to produce the adducts in quantitative yield.





We have not noticed any incidents during grinding reactions under the reaction scale studied. The handling of highly reactive low volatile aromatic nitroolefins in an open petri dish or mortar would not be an apprehension on safety issue since nitroolefins are known to possess antibacerial and antitumor activites.²¹ However, care needs to be taken in handling these materials.

Conclusion

In conclusion, we have demonstrated a simple, atom economy, fast and highly efficient, solvent-free green protocol for synthesis of nitroamines and nitrosulfides. To the best of our knowledge,

 Table 1
 Synthesis of nitroamine derivatives^a

Entry	Nitroalkene	Nucleophile	Method ^b /Time (min)	Product	Yield ^e (%)
1	NO ₂ 2a	NH ₂ la	Method $A/2 + 5$	HN NO ₂ 3a	99
2	2a	NH ₂ 1b	Method A/1 + 5	HN NO ₂ 3b	100
3	2a	NH ₂ OMe	Method B /1 + 0	HN NO ₂ 3c	100
4	2a	() N H	Method $A/1 + 0$	NO ₂ 3d	100
5	NO ₂ NO ₂ 2b	NH ₂ Ia	Method $A/1 + 5$	HN NO_2 $3e$	100
6	2b	NH ₂ 1b	Method A/1 + 5	HN =	100
7	$\bigcup_{NO_2}^{NO_2} 2\mathfrak{c}$	NH ₂ la	Method $A/1 + 5$	$HN = NO_2 \qquad 3g$	100
8	2c	NH ₂ 1b	Method A /1 + 5	$HN = NO_2 \qquad 3h$	100
9	2c	NH ₂ OMe	Method B /1 + 0	HN NO ₂ 3i	100
10	2c	NH ₂ Cl	Method B /3 + 5	HN NO ₂ 3j	98

 Table 1
 (Contd.)



^{*a*} All reactions were carried out with an equimolar (2 mM) ratio of donor and acceptor. 2.2 mM (1.1 equiv) of morpholine (1e) was used in entries 4, 11, 12, and 14. ^{*b*} Method A: mixing of reactants with a spatula in a petri dish for 1–2 min followed by allowing the mixture for standing for 5 min if necessary. Method B: grinding of reactants with a mortar and pestle for 1–3 min followed by allowing the mixture for standing for 5 min if necessary. ^{*c*} Yield of pure Michael adduct.

this green protocol was not known to synthesize aforementioned Michael adducts. The current environmentally benign procedure is a near absolute green protocol since it: (i) does not require the use of solvents (organic or aqueous), catalysts, energy, and purification steps such as column chromatography or crystallization; (ii) requires less time to obtain the products; (iii) incorporates the reactants into the final product to a maximum possible extent without side products; and (iv) stands as the cheapest methodology so far. The success for this technique relies on the selection of Michael donors and acceptors of the reaction. The current novel protocol is a step towards achieving chirality through a green asymmetric approach. Studies in this direction are underway in our laboratory.

Experimental

Reaction between amines and nitroolefins

Solid-liquid combinations: a nitrostyrene (**2a–f**, 2 mmol) and an aniline (**1a–d**, 2 mmol) or morpholine (**1e**, 2.2 mmol) were mixed together thoroughly with a spatula for one to two minutes in a petri dish to form a homogeneous paste and then the mixture was allowed to stand for 5 min if required. The adducts **3a,b,d,e,f,g,h,k,l,m,n,o** were obtained in this way.

Solid-solid combinations: in the case of 1c, the mixture was subjected to mechanical grinding in a mortar with pestle for one min at room temperature to afford adducts 3c,i. The reaction of 1d and 2c was carried out by 3 min of grinding and five min standing at room temperature to get the adduct 3j. Completion of reaction in all the above cases was monitored by TLC.

Reaction between thiols and nitroolefins

A nitrostyrene (2 mmol) and a thiol (2 mmol) were mixed together thoroughly with either (i) a spatula in a petri dish or with (ii) mechanical grinding by a mortar with pestle, for solid-solid reactants for 1–2 min to form a paste. Then the reaction mixture was allowed to stand at room temperature for 5 min. Completion of the reaction was monitored by TLC. The adducts thus obtained, (i) **5a,b,e,f,h,j,k,n,p,q** and (ii) **5c,d,g,i,l,m,o,r**, were characterized by ¹H (500 MHz) and ¹³C (125 MHz) NMR spectroscopy.

Entry	Nitroalkene	Nucleophile	Method ^{<i>b</i>} /Time (min)	Product	Yield ^c (%)
1	NO ₂ 2a	SH 4a	Method $A/2 + 5$	S NO ₂ 5a	98
2	2a	SH 4b	Method $A/1 + 5$	S NO ₂ 5b	100
3	2a	SH 4c	Method B /2 + 5	S NO ₂ 5c	99
4	2a	SH 4f	Method B /1 + 5	S Sd	100
5	NO ₂ NO ₂	SH 4a	Method A /1 + 5	S NO_2 $5e$	100
6	2b	SH 4b	Method $A/1 + 5$	NO_2 S NO_2 Sf	100
7	2b	SH 4c	Method B /1 + 5	S NO ₂ S NO ₂ Sg	100
8	2b	SH OMe 4d	Method $A/1 + 5$	NO_2 S NO_2 OMe S OMe S S OMe S S S OMe S S S S S S S S	100
9	2b	SH Br 4e	Method B /1 + 5	NO ₂ S NO ₂ Br S S S S S	100
10	$\bigcup_{NO_2}^{NO_2} 2c$	SH 4a	Method $A/1 + 5$	NU ₂ S NO ₂ 5j	99

 Table 2
 Synthesis of nitrosulfide derivatives^a



Entry	Nitroalkene	Nucleophile	Method ^b /Time (min)	Product	Yield ^c (%)
11	2c	SH 4b	Method $A/1 + 5$	S NO ₂ Sk	100
12	2c	SH 4c	Method B /1 + 5		100
13	2c	SH Br 4c	Method B /1 + 5	S NO ₂ S S MO ₂ S MO ₂	100
14	Br NO ₂ 2d	SH 4a	Method A /1 + 5	S NO ₂ 5n	100
15	2d	SH 4c	Method B /1 + 5	S Br Br So	100
16	CI NO ₂	SH 4a	Method A /1 + 5	S NO ₂ 5p	100
17	2e	SH 4b	Method A/1 + 5	S CI NO ₂ 5q	100
18	2e	SH 4c	Method B /1 + 5	S CI	100

^{*a*} All reactions were carried out with an equimolar (2 mM) ratio of donor and acceptors. ^{*b*} Method A: mixing of reactants with a spatula in a petri dish for 1-2 min followed by allowing the mixture for standing for 5 min. Method **B**: grinding of reactants with a mortar and pestle for 1-2 min followed by allowing the mixture for standing for 5 min. ^{*c*} Yield of pure Michael adduct.

Acknowledgements

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