# Diastereoselective Synthesis of *syn*-1,3-Dinitro Compounds by Michael Addition of Nitroalkanes to Nitroalkenes with a Thiourea Catalyst

Constantinos Rabalakos, William D. Wulff*

Department of Chemistry, Michigan State University, East Lansing, MI 48824, USA
E-mail: wulff@chemistry.msu.edu

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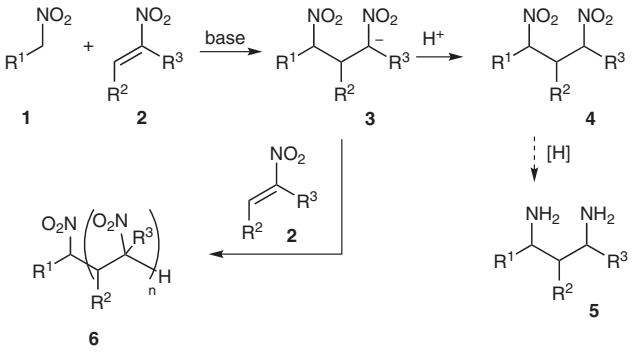
**Abstract:** An operationally simple method has been developed for the conjugate addition of nitroalkanes to β-nitrostyrene with the use of thiourea catalysis. The reaction affords good yields of *syn*-1,3-dinitro adducts with only 2% catalyst loading.

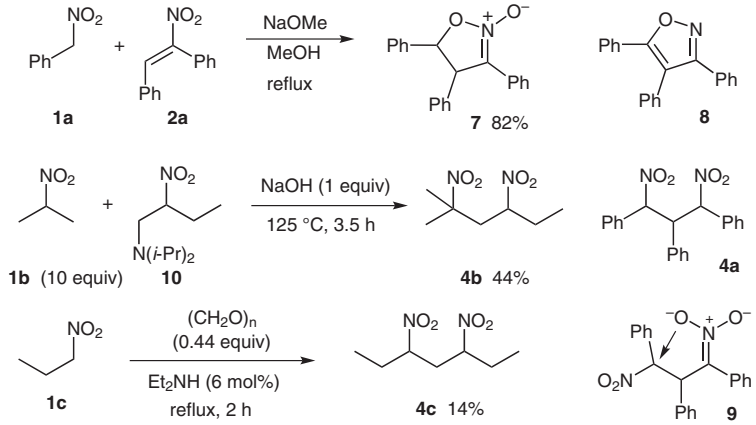
**Key words:** thiourea, organocatalysis, nitroalkene, nitroalkane, diastereoselective, Michael addition

The use of nitroalkanes as reactive nucleophiles[1,2] and the use of nitroalkenes as Michael acceptors[2–5] have attracted significant interest in recent years in carbon–carbon bond-formation reactions. Because of the activating effect of the nitro group, as well as its versatility as a masked functionality, nitro compounds have been quite useful in the synthetic arena.[6] The Michael addition of nitroalkanes to nitroalkenes is particularly interesting because the reaction products (1,3-dinitro compounds) can be easily reduced to 1,3-diamines, a valuable functionality in synthesis of complex molecules, or other 1,3-difunctionalized compounds. Despite its synthetic potential, this reaction has been largely overlooked and is considerably underdeveloped. This is partly because of the difficulty of controlling the addition of a nitronate anion to a nitroalkene (Scheme 1). The initial product formed is the nitronate anion **3**, which is sufficiently reactive to undergo conjugate addition to the nitroalkene and this often results in a mixture of oligomerization products.




**Scheme 1**

One of the earliest reports of the additions of nitroalkanes to nitroalkenes involves the base-induced reaction of phenylnitromethane with nitrostilbene which in refluxing methanol gives the isoxazoline oxide **7** in 82% yield (Scheme 2).[7–9] Depending on the conditions, the isoxazole **8** and the dinitropropane derivative **4a** can also be isolated from this reaction. The evidence suggests that **7** is formed by an intramolecular nucleophilic displacement of a nitrite by an oxygen of the nitronate in intermediate **9**.[8,9c] A number of methods have been developed that involve the in situ generation of the nitroalkene. These include the elimination of a β-amino group[10] as illustrated in the reaction of **10** with 2-nitropropane to give 2-methyl-2,4-dinitrohexane (**4b**).[10b] This can also include a Mannich




**Scheme 2**

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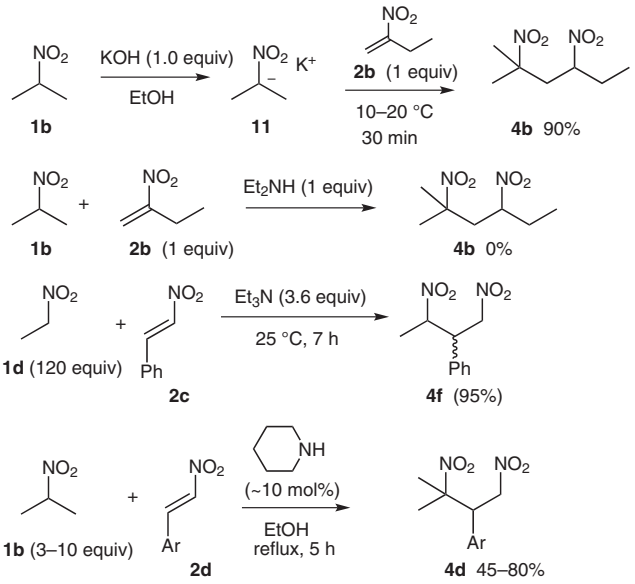
reaction/dehydration as illustrated in the reaction of nitropropane with formaldehyde to give 3,5-dinitroheptane (**4c**).[11] An improved protocol has recently been reported with basic alumina which can be extended to a variety of aldehydes in good yields.[12] Other methods involve β-elimination of a β-acetoxy group[13] and a retro-Mannich reaction.[14]

The most effective protocol that exists to this point involves the stoichiometric generation and addition of a nitronate anion to a nitroalkene.[15,16] This is illustrated by the reaction of 2-nitropropane first with one equivalent of potassium hydroxide and then one equivalent of 2-nitro-1-butene which gives the 2-methyl-2,4-dinitrohexane (**4b**) in 90% yield in 30 minutes at 10–20 °C (Scheme 3).[16] If only 0.25 equivalent of KOH was used in this reaction, **4b** was not observed and only high molecular weight material was obtained and this suggests a slow proton transfer from the nitroalkane to species **3** relative to the reaction of **3** with nitroalkene (Scheme 1). If excess sodium ethoxide was employed in this same reaction, the product of the reaction was the Michael adduct of ethoxide and **2b**. Interestingly, none of the dinitroalkane **4b** was isolated from the reaction mixture if nitroalkane **1b** and one equivalent of nitroalkene **2b** were treated with one equivalent of diethylamine.[16] Successful addition could be achieved without stoichiometric nitronate generation as illustrated by the reaction of nitroethane and nitrostyrene to give **4f** in 95% yield.[17] However, this could only be achieved if a large excess of the nitroalkanes (120 equiv) was employed as the solvent. There are only two examples where a substoichiometric amount of base has been used to catalyze the reaction. One involves the reaction of 2-nitropropane with nitrostyrene derivatives which gave good yields of **4d** with ca. 10 mol% piperidine in refluxing ethanol.[18] Unfortunately, the generality of this process is not clear since this report includes only one nitroalkane and four nitroalkenes of the type **2d** where the aryl group contained either one or two methoxy groups. The other example is of an asymmetric catalytic addition of nitroalkanes to nitrostyrenes mediated by a modified *Cinchona* alkaloid but considerably extended reaction times were required (6–12 d) to effect ten turnovers.[19] Finally, there is an asymmetric version of the reaction that involves the generation of stoichiometric silylnitronates[20] and another that involves a zinc/titanium catalyst complex.[21]

Our approach towards the development of a substoichiometric catalyst for the addition of nitroalkanes to nitroalkenes incorporates the use of thioureas as catalysts.[22] It is known that thioureas can activate nitrostyrene (and other nitroalkenes) for the addition of a variety of nucleophiles.[22] On the other hand, the activation of nitroalkanes and the enhancement of their acidity through their interaction with thioureas is also known, in several reports where the successful employment of nitroalkanes as reactive nucleophiles is described[22]. Despite all of these reports, a thiourea-promoted addition of nitroalkanes to nitroalkenes has never been reported in the literature. Herein we




**Scheme 3**

describe a method where thioureas can greatly accelerate the Michael addition of nitroalkanes to nitroalkenes where the reaction is not plagued by the problem of the oligomerization and affords a variety of *syn*-1,3-dinitro compounds with good yields and diastereoselectivities.

We started our investigation by using the reaction between *trans*-β-nitrostyrene (**2c**) and 1-nitropropane (**1c**) as a model reaction in $CDCl_3$, applying only five equivalents of nitropropane and using 10 mol% of the thiourea catalyst (see Figure 1) and 10 mol% triethylamine. As can be seen in Scheme 4, the reaction without a thiourea catalyst (using 10 mol% $Et_3N$) was very slow, affording only 5% yield after three hours. On the other hand, the rate acceleration that thioureas **12**,[23] **13**, and **14** (Figure 1) caused is very significant: thioureas **13** and **14** could increase the relative rate of the reaction approximately five and six times, respectively, while it is obvious that thiourea **12**, bearing the 3,5-bis(trifluoromethyl) moiety was the most efficient catalyst, leading to almost quantitative conversion of the starting nitrostyrene in two hours, and affording a ca. 60% yield of the desired 1,3-dinitroalkane **4e**.

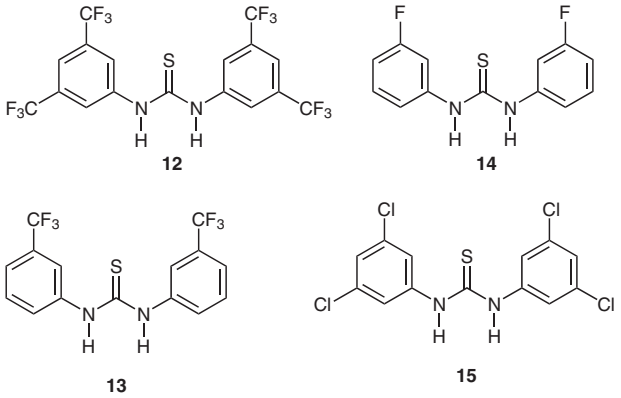
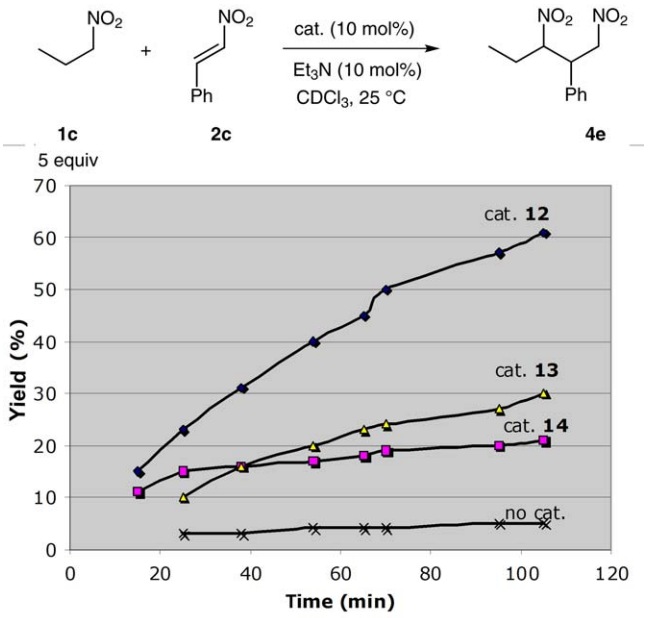



**Figure 1**

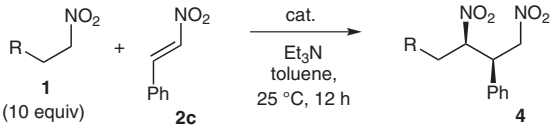



**Scheme 4** Acceleration of the Michael addition of **1c** to **2c** by thiourea catalysts

Next, the efficiency of thioureas **12**–**15** (Figure 1) was investigated with respect to the yield and the diastereoselectivity of the transformation. The results for the reaction of nitroethane, 1-nitropropane and 1-nitrobutane with nitrostyrene **2c** are shown in Table 1. As the data reveals, nitroethane afforded a nearly equal mixture of diastereomers (entry 1), but for the other nitroalkanes the control of the selectivity was much better. All of the thioureas controlled the selectivity of the reaction in favor of the *syn*-isomer, furnishing the desired product in good yields (up to 83%) and affording dr ratios between 77:23 and 87:13. The background reaction without a thiourea (10% $Et_3N$, entry 6) was very slow, leading only to a trace of product after an overnight period, while it was interesting to observe that in the absence of thiourea, even a stoichiometric amount of base was still inefficient in promoting the reaction and furnished a 39% yield with a slight preference for the *anti*-isomer, revealing that the catalytic and the background reaction complement each other in terms of stereocontrol. Finally, the reaction with 1-nitrobutane (entry 8) was consistent with the rest, giving 82% yield of *syn*-enriched product.

Since catalyst **12** was identified as optimal for this reaction, the addition of 1-nitropropane to nitrostyrene catalyzed by thiourea **12** was examined in different solvents and using various catalyst loadings and the results are summarized in Table 2. Apparently the diastereoselectivity of the reaction remained intact when the amount of catalyst was reduced to 2 mol%, while a small drop-off was observed on the yield of the reaction (entry 3, 58%). This could be reversed by adding more nitropropane or by increasing the reaction time. Using 20 equivalents of nitroalkane and keeping the catalyst loading at 2 mol%, a very good yield of the product could be obtained (85%, entry 4) while there was no decrease in the *syn* to *anti* ratio. The reaction in other solvents also afforded good yields and diastereoselectivities, with THF being the only exception. This might not be so unexpected for a solvent that can function as an H-bond acceptor and compete with the substrate for the catalyst.

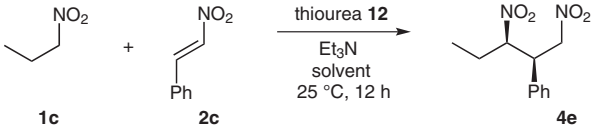
**Table 1** Michael Addition to Nitrostyrene by Thiourea catalysts **12**–**15**[a]




| Entry | R | Cat. (%) | $Et_3N$ (%) | Yield (%)[b] | dr[c] (*syn*/*anti*) |
|---|---|---|---|---|---|
| 1 | H | **12** (10) | 10 | 85 | 55:45 |
| 2 | Me | **12** (10) | 10 | 83 | 77:23 |
| 3 | Me | **13** (10) | 10 | 66 | 78:22 |
| 4 | Me | **14** (10) | 10 | 58 | 87:13 |
| 5 | Me | **15** (10) | 10 | 75 | 80:20 |
| 6 | Me | – (0) | 10 | 7 | n.d. |
| 7 | Me | – (0) | 100 | 39 | 40:60 |
| 8 | Et | **12** (10) | 10 | 82 | 77:23 |

[a] Reaction was conducted in toluene at 0.22 M in **2c** for 12 h with nitroalkane (10 equiv).
[b] Isolated yield of the mixture of diastereomers.
[c] Determined by HPLC analysis.

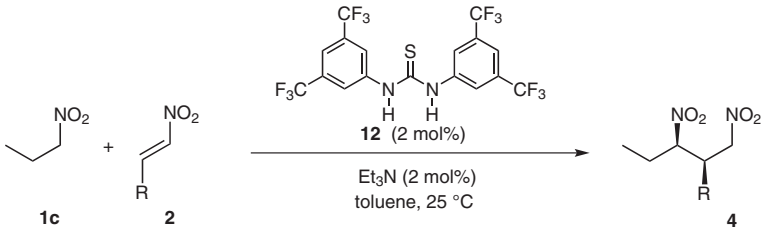
**Table 2** Examination of Solvents and Catalyst Loading with Thiourea **12**[a]




| Entry | Solvent | **12** (%) | $Et_3N$ (%) | *n*-$PrNO_2$ (equiv) | Yield (%)[b] | dr[c] |
|---|---|---|---|---|---|---|
| 1 | toluene | 10 | 10 | 10 | 83 | 77:23 |
| 2 | toluene | 4 | 4 | 10 | 63 | 80:20 |
| 3 | toluene | 2 | 2 | 10 | 58 | 79:21 |
| 4 | toluene | 2 | 2 | 20 | 85 | 77:23 |
| 5 | – | 2 | 2 | 20 | 82 | 73:27 |
| 6 | benzene | 10 | 10 | 10 | 89 | 68:32 |
| 7 | $CH_2Cl_2$ | 10 | 10 | 10 | 78 | 75:25 |
| 8 | THF | 10 | 10 | 10 | 45 | 77:23 |

[a] Reactions were conducted in the proper solvent at 0.22 M in **2c**, for 12 h.
[b] Determined by $^1H$ NMR of the crude mixture.
[c] Determined by HPLC analysis assuming equal extinction coefficients for each diastereomer.

**Table 3** Reaction Scope for the Thiourea-Catalyzed Addition of **1c** to Nitroalkenes[a]




| Entry | R | Adduct | Overall yield (%)[b] | Yield (%) *syn*[c] | dr[d] |
|---|---|---|---|---|---|
| 1 | Ph | **4e** | 87 | 75 | 86:14 |
| 2 | 4-$MeOC_6H_4$ | **4g** | 82 | 73 | 88:12 |
| 3 | 2-$MeOC_6H_4$ | **4h** | 83 | 66 | 80:20 |
| 4 | 4-$MeC_6H_4$ | **4i** | 72 | 56 | 77:23 |
| 5 | 2-$ClC_6H_4$ | **4j** | 80 | 68 | 85:15 |
| 6 | 4-$ClC_6H_4$ | **4k** | 73 | 58 | 80:20 |
| 7 | 4-$BrC_6H_4$ | **4l** | 66 | 57 | 85:15 |
| 8 | 3-$BrC_6H_4$ | **4m** | 75 | 69 | 90:10 |
| 9 | 2-$BrC_6H_4$ | **4n** | 66 | 60 | 90:10 |

[a] Reactions were performed with **1c** (20 equiv) at 0.22 M in **2** in toluene for 16 h except entries 2–4 where the reaction time was 40 h.
[b] The sum of the isolated yields of *syn*- and *anti*-isomers which were separated by silica gel chromatography.
[c] Isolated yield after column chromatography on silica gel.
[d] Ratio of the isolated yields of the *syn*- to *anti*-isomers.

After the above study, the conditions in Table 2, entry 4 were chosen as the optimum and the scope of the reaction was examined for a series of substituted nitrostyrenes. As can be seen by the data in Table 3, a variety of electronically diverse nitrostyrenes underwent the thiourea-catalyzed addition to give the *syn*-1,3-dinitro adducts **4e**, **g–n** in good yields. Electron-rich nitrostyrenes (entries 2–4) were less reactive and needed longer reaction times (40 h) to go to completion, while electron-deficient substrates (entries 5–8) afforded complete conversions in only 16 hours. In every case, the starting material underwent complete conversion and only small amounts of polymer were formed. These reactions were in general very clean and fast compared to those without the thiourea catalyst. It seems that the thiourea catalyst both accelerates the formation of the desired adducts while suppressing the multiple addition process and overall displays very good turnover frequency. Additionally, the thiourea catalyst **12** favors the formation of the *syn*-diastereomer in good selectivities that range from 3:1 to 9:1.

In summary, an efficient protocol for the stereoselective conjugate addition of nitroalkanes to nitroalkenes has been developed. To the best of our knowledge this is the most efficient method yet reported for the preparation of *syn*-1,3-dinitro compounds from the catalytic (substoichiometric) addition of nitroalkanes to nitroalkenes. The method is operationally very simple and only 2 mol% of catalyst is required, while good yields and selectivities are obtained for a number of substituted nitrostyrenes. We are currently exploring the development of an asymmetric version of this reaction using chiral thioureas and will report the results separately in due course.

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