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## Graphical Abstract

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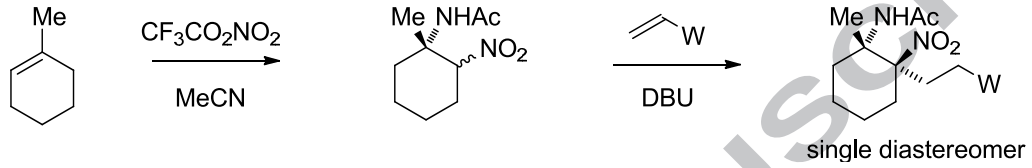

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# Synthesis and conjugate addition reactions of *N*-(βnitroalkyl)amides

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ABSTRACT

Nitration of several di- and trisubstituted alkenes with lithium nitrate / TFAA in nitrile solvents afforded *N*-(βnitroalkyl)amides in 28-72% yield. Nitration of 1,1-diphenylethene gave 1,1-diphenyl-2-nitroethene in 52% yield instead of the *N*-(βnitroalkyl)amide. Reaction of 1-methylcyclohexene using excess lithium nitrate / TFAA in acetonitrile gave a single diastereomer of *N*-(2,6-dinitro-1-cyclohexyl)acetamide in 55% yield. *N*-(βNitroalkyl)amides undergo diastereoselective Michael addition to a variety of Michael acceptors. Diastereoselectivity is rationalized on the basis of internal hydrogen-bonding within the intermediate nitronate resulting in a strongly-biased Michael donor conformation.



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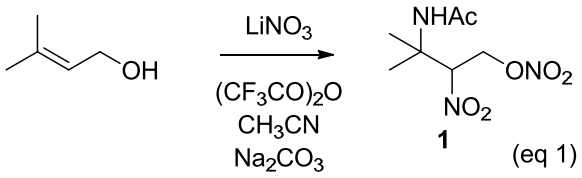
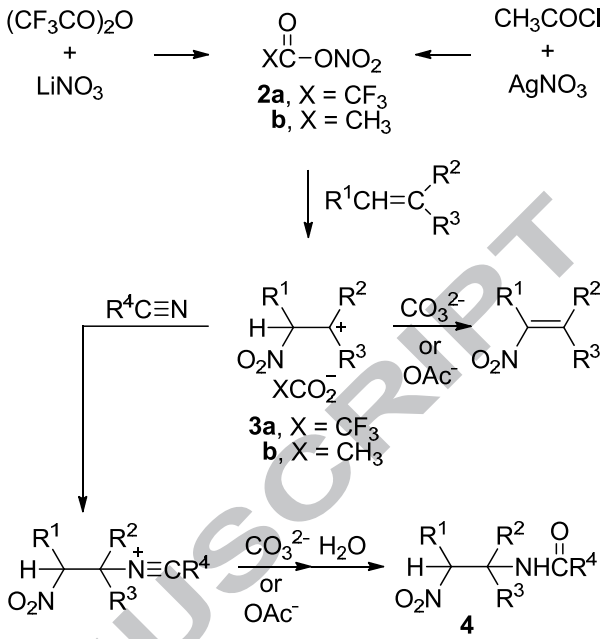
*N*-(βnitroalkyl)amides are difunctional compounds that are not naturally occurring and have been relatively little studied. Sporadic reports[1] of their preparation exist, but no systematic studies have been documented. Our initial interest in these compounds arose serendipitously. An attempt to convert the alcohol 3-methylbut-2-en-1-ol to its nitrate ester using nitration conditions developed by Skrydstrup *et al.*[2] led to concomitant reaction at the C,C-double bond: the *N*-(βnitroalkyl)acetamide **1** was obtained in 75% yield (eq 1).

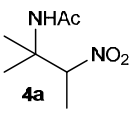
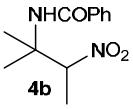
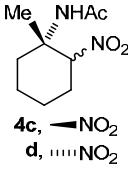
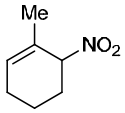
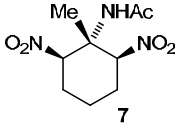


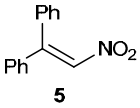
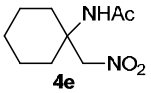

From the above result, it was apparent that appropriate simple alkenes would likely afford *N*-(βnitroalkyl)acetamides under similar nitration conditions. Indeed, a series of alkenes was converted to the corresponding *N*-(βnitroalkyl)acetamides **4a**, and **4c-e** under the nitration conditions recommended by Skrydstrup *et al.*[2] (Table 1). Specifically, trifluoroacetic anhydride (TFAA) is added to an acetonitrile solution of lithium nitrate and the resulting solution is cooled after 30 minutes to 0-5 °C.[3] Anhydrous sodium carbonate is added and then the alkene. These reaction conditions are convenient and the reagents are inexpensive. The likely mechanistic pathway involves trifluoroacetyl nitrate (**2a**) as the putative nitrating agent and is shown in Scheme 1. It is proposed that the intermediate β nitrocarbocation ion pair **3a** is trapped by nitrile solvent to form a nitrilium ion in a process akin to the Ritter reaction. Previously




**Scheme 1**. Mechanism for formation of Aβnitroalkyl)amides

**Table 1.**
Nitration products of alkenes[a]

| Entry | $R^1CH=CR^2R^3$ $R^1$ $R^2$ $R^3$ | | | $XONO_2$ | $R^4CN$ | Temp, °C | *N*-(β-nitro-alkyl)amide | Diastereomer ratio | Yield, % | Other products | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Me | Me | Me | $CF_3CO_2NO_2$ | MeCN | 0-5 |  **4a** | | 72 | | |
| 2[b] | Me | Me | Me | $CF_3CO_2NO_2$ | PhCN | 0-5 |  **4b** | | 28 | | |
| 3[c] | -$(CH_2)_4$- | | Me | $CF_3CO_2NO_2$ | MeCN | 0-5 |  **4c**, —$NO_2$ **d**, ⋯$NO_2$ | **4c,d** 1:1 | 35 |  **6** | 41 |
| 4[d,e] | -$(CH_2)_4$- | | Me | $AcONO_2$ | MeCN | 60-65 | **4c,d** | **4c,d** 4:1 | 35 | **6** | 48 |
| 5[d] | -$(CH_2)_4$- | | Me | $AcONO_2$ | MeCN | 60-65 | **4c,d** | **4c,d** 2.3:1 | 33 | **6** | 39 |
| 6[d] | -$(CH_2)_4$- | | Me | $AcONO_2$ | MeCN | 0-5 | **4c,d** | **4c,d** 1.5:1 | 36 | **6** | 42 |
| 7 | -$(CH_2)_4$- | | Me | $CF_3CO_2NO_2$ | MeCN | 0-5 | | | |  **7** | 55 |

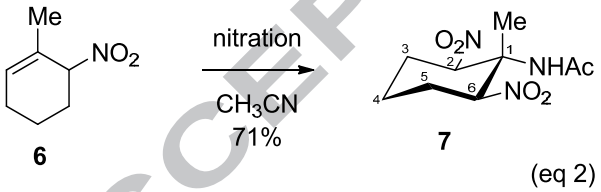
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 8 | H | Ph | Ph | $CF_3CO_2NO_2$ | MeCN | 0-5 |  **5** | 52 |
| 9[f] | H | $-(CH_2)_3-$ | | $CF_3CO_2NO_2$ | MeCN | 0-5 |  **4e** | 68 |

[a]General procedure[3] unless otherwise indicated. [b]In 50:50 PhCN / $Et_2O$. [c] $LiNO_3$ / $(CF_3CO)_2O$ (1 eq) ). [d] $AgNO_3$ / AcCl (1 eq) in MeCN. [e]Results from reference 1b. [f] Alkene added dropwise over 10 min

nitration of several alkenes with acetyl nitrate (**2b**), prepared from silver nitrate / acetyl chloride, in acetonitrile was shown to afford *N*-(βnitroalkyl)acetamides.[1b] The mechanistic pathways are presumably closely related.

Several variations to the reaction conditions were briefly examined. Sodium carbonate can be replaced by milder bases. Both sodium bicarbonate and sodium acetate give analogous results if sufficient excess (4 equivalents) is employed. It was possible to replace acetonitrile by 1:1 benzonitrile / ethyl ether and readily obtain the *N*-(βnitroalkyl)benzamide **4b** although in only 28% yield (entry 2). However, amide formation does not always occur: nitration of 1,1-diphenylethene under a variety of conditions gave only 1,1-diphenyl-2-nitroethene (**5**) and none of the *N*-(βnitroalkyl)acetamide (entry 8).

Normally excess nitrating agent (formed from 1.8-2 equiv TFAA) was used to ensure complete reaction of the alkene. However, 1-methylcyclohexene gave *N*-(β,β-dinitroalkyl)acetamide **7** under these conditions (entry 7). When less nitrating agent (formed from 1 equiv TFAA; entry 3) was used, *N*-(βnitroalkyl)acetamide **4c,d** (1:1 diastereomer mixture) was obtained accompanied by 1-methyl-6-nitrocyclohexene (**6**). Nitrocycloalkene **6** could be further nitrated to give *N*-(β,β-dinitroalkyl)acetamide **7** in 71% yield implicating **6** as an intermediate in the dinitration of 1-methylcyclohexene (eq 2). That **7** was a meso stereoisomer was readily apparent from its $^{13}C$ NMR spectrum (only 7 signals). Compound **7** appears to be

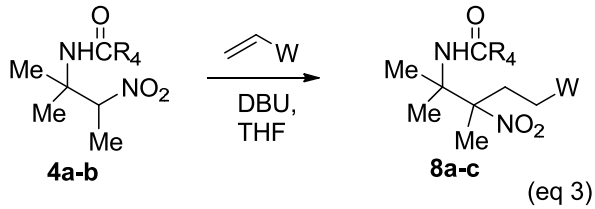



(eq 2)

the (1*r*, 2*R*, 6*S*)-isomer based on NOE spectra. The overlapping signal attributed to both axial and equatorial H-3, H-5 protons is enhanced upon saturation of the C-1 methyl protons.

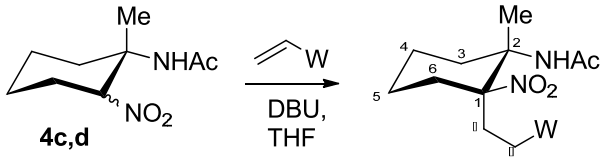
Nitration of 1-methylcyclohexene using silver nitrate / acetyl chloride in acetonitrile at 65 °C was reported[1b] to give *N*-(β nitroalkyl)acetamide **4c**,**d** in 35% yield (entry 4; 4:1 mixture of diastereomers, major isomer undetermined but the reported spectrum matches **4c**) and nitrocycloalkene **6** in 48% yield. We were unable to duplicate the published product ratio, but did observe differing ratios dependent on temperature. Using silver nitrate / acetyl chloride at 0-5 °C afforded **4c**,**d** in a 1.5:1 ratio (structures of **4c**,**4d** assigned from NOE studies). At 60-65 °C the ratio was 2.3:1. In both cases, the major isomer was **4c** and nitrocycloalkene **6** predominated (entries 5 and 6). The reason for the differing product ratios as a function of nitration conditions is unclear. The 1:1 **4c**,**d** isomer ratio obtained using lithium nitrate /TFAA was independent of the base: sodium carbonate, sodium bicarbonate, and sodium acetate gave identical results. Consequently, base is not catalyzing isomer interconversion. A simple carbocation intermediate should give a common product isomer ratio. It is hypothesized that ion pairs **3a-b** are the actual intermediates and **3b** leads somewhat more preferentially to diastereomer **4c**.

We have begun an extensive study of the chemistry of *N*-(β nitroalkyl)amides. These compounds readily undergo condensation reactions with a variety of Michael acceptors in the presence of DBU (eqs 3-4; Table 2).[4-7] The Michael adducts are highly functionalized and should be robust intermediates for synthesis. Of particular interest are the results for the chiral *N*-(β nitroalkyl)acetamide **4c**,**d**. A diastereomeric mixture of **4c**,**d** underwent reactions with methyl acrylate, acrylonitrile, and 3-buten-2-one to give Michael adducts **9a-c** as single diastereomers (eq 4).




(eq 3)

The structure of **9a** was initially determined from NMR spectral data. There is long-range coupling (W-coupling) between axial H-6 and one of the side-chain H-βprotons requiring axial placement of the side chain[8] NOE enhancement from axial H-4 to the C-1 methyl protons indicated axial placement of the methyl group. Crystallization of **9a** readily



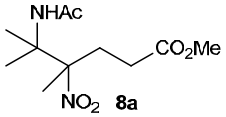
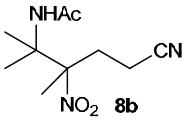
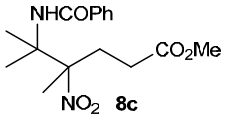
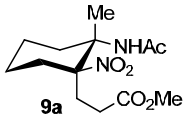
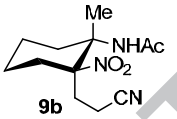
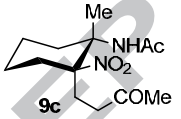

**9a**, W = $CO_2Me$
**b**, W = CN
**c**, W = COMe

(eq 4)

occurs, but the crystals are poorly formed and include a water of hydration. Repeated attempts provided a crystal sufficient for X-ray analysis and the structure of **9a** was confirmed. Likewise, adducts **9b**-**c** were obtained as single diastereomers and exhibit the same long range coupling between H-6 and one of the side-chain H-βprotons.

It seems likely that the high observed diastereoselectivity in these reactions arises as a result of internal hydrogen bonding in the Michael donor, a nitronate intermediate. This internal H-bonding is presumably between the amide proton (donor) and

**Table 2.**
Michael adducts obtained from *N*-(βnitroalkyl)amides[a]

| *N*-(β-Nitro-alkyl)amide | Adduct | Yield, % | Diastereomer ratio |
|---|---|---|---|
| 4a |  **8a** | 58 | |
| 4a |  **8b** | 55 | |
| 4b |  **8c** | 81 | |
| 4c,d |  **9a** | 61 | >98:2[b] |
| 4c,d |  **9b** | 61 | >98:2[b] |
| 4c,d |  **9c** | 54 | >98:2[b] |

[a] After 14 h at 20 °C using DBU in THF. [b]Estimated by NMR.

a nitronate O-atom (acceptor). As a result of internal H-bonding, the nitronate populates one relatively rigid predominant conformation. For example, formation of Michael adduct **9a** would be dictated by constrained axial attack of the H-bonded Michael donor on methyl acrylate (Figure 1).

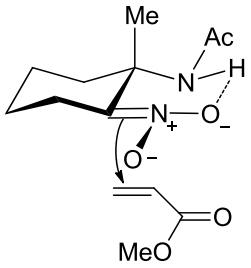
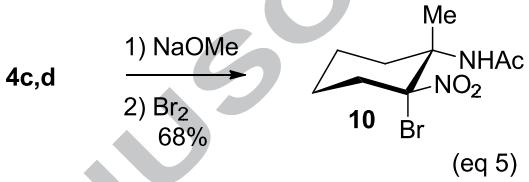


**Figure 1**. Michael reaction of methyl acrylate with the internally H-bonded nitronate formed from **4c,d**

There have been many reports of high enantioselectivity attributed to H-bonding with appropriate chiral catalysts in Michael reactions.[9] However, diastereoselectivity is not always high in Michael reactions.[10] To our knowledge, high diastereoselectivity arising from internal H-bonding in the Michael donor itself has not previously been described.

Consistent with the hypothesized internal H-bonding in the nitronate formed from **4c,d**, bromination of **4c,d** also affords a single isomer of the αbromonitro compound **10** isolated in 68% yield (eq 5). The assignment of likely stereochemistry is based by analogy to the Michael adducts. It is thought that internal H-bonding in the nitronate intermediate results in diastereoselective reaction.




Studies to determine further synthetic transformations of *N*-(βnitroalkyl)amides are ongoing and will be reported at a later time.

## Supplementary material

Experimental procedures, NMR spectral data for all new compounds, and X-ray crystallographic data for **9a** can be found at http//.

## Acknowledgment

One of us (JL) wishes to thank Drs. Bruce and Cynthia Maryanoff for providing a summer undergraduate research fellowship supporting this work.

## References and Notes

1. For example, see: (a) Scheinbaum, M. L.; Dines, M. *J. Org. Chem.* **1971**, *36*, 3641-3642. (b) Kancharla, P. K.; Reddy, Y. S.; Dharuman, S.; Vankar, Y. D. *J. Org. Chem.* **2011**, *76*, 5832-5837. (c) *J. Chem. Soc., Perkin Trans. 1* **1984**, 2357. (d) Bach, R. D.; Holubka, J. W.; Badger, R. C.; Rajan, S. J. *J. Am. Chem. Soc.* **1979**, *101*, 4416-4417. (e) Desai, M. C.; Thadeio, P. F. Lefkowitz, S. L. *Tetrahedron Lett.* **1993**, *34*, 5831. (f) Turner, W. B. *J. Chem. Soc. C* **1967**, 2225-2228.

2. Gavrilla, A.; Andesen, L.; Skrydstrup, T. *Tetrahedron Lett.* **2005**, *46*, 6205.

3. The general procedure for preparation of *N*-(β-nitroalkyl)-acetamides was as follows. TFAA (4.2 g, 0.02 mol) was added to a solution containing $LiNO_3$ (2.5 g, 0.036 mol) in acetonitrile (40 mL) and the resulting solution was stirred for 30 min at ambient temperature. The solution was cooled (0-5°C) and layered with anhydrous $Na_2CO_3$ (2.12 g, 0.02 mol). The mixture was stirred for 30 min and alkene (0.01 mol) was added. The resulting cold mixture

was stirred for 12 h and was then poured into water (50 mL). Extraction with $CH_2Cl_2$ (three 50-mL portions) gave a combined organic layer which was dried over anhydrous $MgSO_4$. Concentration under reduced pressure gave crude product. Compound **4a** was readily crystallized by dissolving the crude product in warm $CHCl_3$ and adding a volume three times greater of warm toluene. On cooling, purified solid **4a** was obtained. All other crude *N*-(β-nitroalkyl)acetamides were purified by flash chromatography. The resulting viscous oils were crystallized by the same method used for **4a** except for **1** which did not crystallize.

4. For a general discussion of the Michael reaction, see: Smith, M. B. "March's Advanced Organic Chemistry", 7th edition, Wiley: Hoboken NJ, 2013, pp 943-949.

5. For a recent review of the Michael reaction involving nitronates as the donor, see: Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.*, **2005**, *105*, 933-971.

6. The following general procedure was used to prepare Michael adducts **8a**, **8c**, and **9a**. DBU (0.17 g, 1.1 mmol) was added to a solution of methyl acrylate (0.10 g, 1.1 mmol) and *N*-(βnitroalkyl)amide (1 mmol) in THF (1 mL). The resulting solution was stirred for 18 h and was diluted with $CH_2Cl_2$ (20 mL). The diluted solution was washed with 1.2 M hydrochloric acid (10 mL) followed by brine (10 mL) and was dried over anhydrous $MgSO_4$. Concentration at reduced pressure gave crude product. Michael adducts **8a** and **9a** were crystallized by first dissolving in warm $CHCl_3$ and adding a volume three times greater of warm toluene. On cooling, pure products were obtained. Michael adduct **8c** was purified by flash chromatography.

7. To prepare Michael adducts **8b** and **9b**, the preceding general procedure (footnote 6) was followed except acrylonitrile (0.06 g, 1 mmol) replaced methyl acrylate. The crude products were crystallized from absolute ethanol. To prepare Michael adduct **9c**, the general procedure was modified by replacing methyl acrylate with 3-buten-2-one (1 mmol) and the crude product was purified by flash chromatography.

8. This W-coupling parallels axial W-coupling reported for the angular methyl signal of *trans*-5βhydroxy-10βmethyl-2-decalone and related compounds: Williamson, K. L.; Howell, T.; Spencer, T. A. *J. Am. Chem. Soc.* **1966**, *88*, 325-334.

9. Selected reviews include: (a) Vicario, J. L.; Reyes, E.; Carrillo, L.; Uria, U. in "Comprehensive Organic Synthesis", 2nd Edition, Knochel, P.; Molander, G. A., Eds; Elsevier: Amsterdam, The Netherlands, 2014;Vol. 4, pp 119-188 (b) Fang, X.; Wang, C.-J. *Chem. Comm.* **2015**, *51*, 1185-1197. (c) Roca-Lopez, D.; Sadaba, D.; Delso, I.; Herrera, R. P.; Tejero, T.; Merino, P. *Tetrahedron Asymmetry* **2010**, *21*, 2561-2601. (d) Heravi, M. M.; Hajiabbasi, P.; Hamidi, H. *Curr. Org. Chem.* **2014**, *18*, 489-511.

10. For example, see: Ooi, T.; Fujioka, S.; Maruoka, K. *J. Am. Chem. Soc.,* **2004**, *126*, 11790-11791.