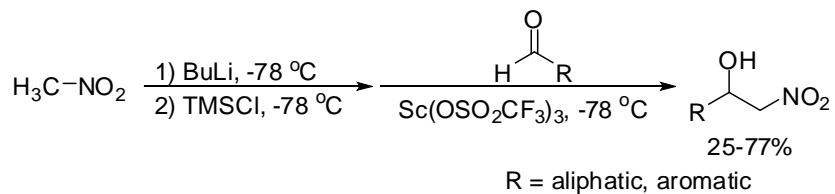


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The first example of trimethylsilyl methylenenitronate reacting with aldehydes under an apparent Mukaiyama nitro-aldol reaction

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ARTICLE INFO

Article history:

Received

Received in revised form

Accepted

Available online

Keywords:

Mukaiyama nitro-aldol

1,2-Nitroalcohol

Henry reaction

Silyl nitronate

Scandium triflate

ABSTRACT

Trimethylsilyl methylenenitronate reacts with both aliphatic and aromatic aldehydes in the presence of catalytic amounts of scandium(III) triflate to form the Henry reaction products in low (25%) to good yields (77%). This is the first example of this silyl nitronate undergoing a nitro-aldol reaction under an acid environment.

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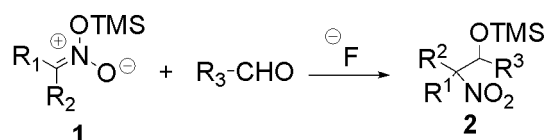
1. Introduction

The Henry reaction¹ is a classic carbon-carbon bond forming reaction between a nitronate and an aldehyde or ketone that generates a β -nitroalcohol. The reaction product is amendable to further transformation. For example, reduction of the nitro group to an amine² or the conversion of the nitro group into a carbonyl functionality (Nef Reaction),³ makes the Henry reaction products useful intermediates in the synthesis of a wide variety of natural products and medicinally important compounds.⁴

One of the drawbacks of this reaction is that it often produces low yields of the β -nitroalcohol product because of the favoured retro Henry reaction.^{4,5} To overcome the attenuated yield, the nitroalkane is used in large excess (5–10 mole excess) compared to the number of equivalents of aldehyde,⁶ which greatly reduces the synthetic utility of this reaction. A significant number of different reaction conditions, all using basic reagents,⁷ have been reported in an attempt to improve the yield of this reaction.⁸ Unfortunately, under basic conditions, the β -nitroalcohol formed can eliminate water yielding a nitroalkene. This is a significant problem when aromatic aldehydes⁹ are used within the reaction. Also, other undesirable base catalysed reactions involving aldehydes, such as aldol condensation,¹⁰ Cannizzaro reaction¹¹ and/or Tishchenko reaction,¹² may occur during the reaction to further reduce the yield of the β -nitroalcohol.

Silyl nitronates were first used within the Henry reaction by Seebach in 1978¹³ and have appeared sporadically in the literature since this initial report.¹⁴ Major benefits of using silyl nitronates include trapping the Henry reaction products to prevent the retro reactions from occurring, the equimolar amounts of silyl nitronate to reacting aldehyde and the lack of reactivity of the β -nitroalcohol product to form the nitroalkene. All of the reported examples of the Henry reaction with silyl nitronates use an anhydrous fluoride source to initiate the

reaction. This fluoride source is not commercially available and must be prepared.¹⁴ It is believed that the fluoride anion reacts with the silyl nitronate **1** to liberate the anionic nitronate that reacts with the aldehyde present in the reaction. The resulting alkoxide undergoes reaction with a TMS source in the reaction mixture to afford the protected β -nitroalcohol **2**.



Scheme 1: The Henry reaction of a silyl nitronates with an aldehyde in the presence of a catalytic amount of a fluoride source.

Recently, a ‘push-pull’ methodology reported on a combined Lewis acid catalyst with an anhydrous fluoride source.¹⁵ Unfortunately, under these reaction conditions the nitroalcohol products could not be isolated and therefore were isolated as the Mosher ester decreasing the synthetic utility of this procedure. It is disclosed herein, a study that investigates the use of an acidic reaction conditions in the Henry reaction to produce the β -nitroalcohol product.

2. Results and discussion

Calculations completed using the Gaussian 2003 software package¹⁶ at the Hartree-Fock level of theory, using the 631-G* basis set, shows that the alkene carbon of the nitronate contains about half of the electron charge of the corresponding carbon in

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the silyl enol ether (Fig. 1). These calculations show that the alkene carbon in the nitronate does contain a negative charge, albeit a smaller charge than silyl enol ether, and still should react with electrophilic species.

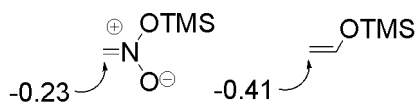


Figure 1: Calculated charge on the nucleophilic carbon atom of silyl enol ether and the corresponding silyl nitronate

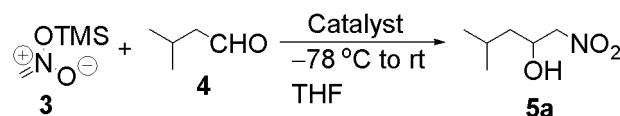
Based on this theoretical data, a survey of Lewis acid catalysts that are typically used in Mukaiyama aldol reactions was undertaken in the reaction between isovaleraldehyde **4** and trimethylsilyl methylenenitronate **3**, the simplest silyl nitronate (Table 1). Surprisingly, this silyl nitronate has not been used in the Henry reaction to date. Typically, the substituted silyl nitronates that have been used are isolated and purified before the Mukaiyama nitro-aldol is performed.¹⁷ All attempts to isolate nitronate **3** before performing any experiment failed. When the crude material was attempted to be purified by vacuum distillation, it turned from a clear colorless liquid to a white insoluble material. However, this silyl nitronate has been reported to be formed *in situ* and used without further purification.¹⁸ Therefore, it was decided to generate trimethylsilyl methylenenitronate **3** *in situ* by reacting nitromethane with *n*-butyl lithium and quenching the resulting anion with trimethylsilyl chloride. *n*-Butyl lithium was chosen as the base to ensure that the conjugate acid from the acid-base reaction would not affect the chemistry that was being investigated.

Two Lewis acids that were originally reported by Mukaiyama¹⁹ to effectively initiate the aldol reaction, aluminum chloride (Table 1, entries 1 and 2) and, titanium(IV) chloride (Table 1, entries 3 and 4) gave no product or a low yield of the β -nitroalcohol depending on the amount of the Lewis acid used within the reaction conditions. $\text{BF}_3 \cdot \text{OEt}_2$ (Table 1, entry 7–9), also reported in Mukaiyama's original paper, gave its best yield when used in only 5 mole %. Even though $\text{Cu}(\text{OTf})_2$ (Table 1, entries 12 and 13) has been successful in promoting the Mukaiyama aldol recently,²⁰ it only afforded the β -nitroalcohol in 20% yield when added in a molar equivalent to the nitronate. The $\text{Ti}(\text{O}i\text{Pr})_4$ ²¹ afforded no β -nitroalcohol when added in equimolar portions but generated 55% of the desired Henry product when added in only 5 mole %. Stannous chloride²¹ gave low yields of the β -nitroalcohol when added in 5 mole % but it was scandium(III) triflate that gave the best yield of the desired Henry reaction product (68%). It should be noted that when this Lewis acid was added in a molar equivalent the aldehyde was consumed to produce intractable polar material.

From the results obtained in the preliminary Lewis acid screen, the methodology was tested further by reacting various aldehydes with **3** in the presence of scandium(III) triflate (Table 2). It was found that the reaction conditions did not require the temperature to be raised to room temperature in order for the reaction to go to completion (Table 2, entry 1). Thus all of the reactions could be completed at -78°C . It was reasoned that keeping the reaction mixture at -78°C would prevent possible side reactions from occurring. Following generation of **3**, five mole percent of scandium(III) triflate in THF was introduced, immediately followed by addition of the aldehyde. Reactions were monitored by TLC. The reaction time (Table 2) indicates

the time for the starting aldehyde to be consumed or no further change occurred as judged by TLC. All reactions that contained aliphatic aldehydes went to completion, however, after work up and purification procedures, the aldehyde reappeared on TLC experiments.

Table 1. Lewis acid screen for the Mukaiyama nitro-aldol reaction



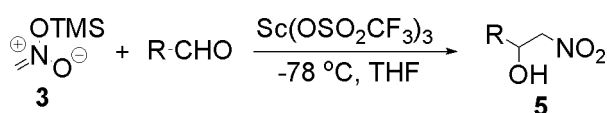
Entry	Catalyst	Mol %	Yield (%)
1	AlCl_3	100	0
2		5	5
3	TiCl_4	100	0
4		5	7
5	$\text{Ti}(\text{O}i\text{Pr})_4$	100	0
6		5	55
7	$\text{BF}_3 \cdot \text{OEt}_2$	100	12
8		5	40
9	SnCl_2	100	14
10		5	42
11	$\text{Cu}(\text{OSO}_2\text{CF}_3)_2$	100	20
12		5	6
13	$\text{Sc}(\text{OSO}_2\text{CF}_3)_3$	100	0
14		5	68

The reaction of trimethylsilyl methylenenitronate with various aldehydes afforded the β -nitroalcohol products in low (25%) to good (77%) yields. Reaction of both aliphatic aldehydes (Table 2, entries 1–6) and aromatic aldehydes (Table 2, entries 7–13) gave comparable outcomes. Four of the six aliphatic substrates (isovaleraldehyde, trimethylacetaldehyde, hexanal, and hydrocinnamaldehyde) gave moderate yields (53–68%). The low yield obtained of 1-cyclohexyl-2-nitroethanol **5c** (Table 2, entry 3) and 3-methyl-1-nitropentane-2-ol **5f** (Table 2, entry 6) cannot be explained through steric factors because of the larger yield obtained for 1-*t*-butyl-2-nitroethanol **5b**. This data indicate that a secondary carbon alpha to the carbonyl functionality lowers the yield of the desired Henry reaction product. It should be noted that the reaction for these two substrates was repeated and the yield of the β -nitroalcohol was comparable.

Aromatic aldehydes also afforded the β -nitroalcohol product, although the reaction times were slightly longer than the aliphatic aldehydes and a very small amount of aldehyde always remained, as evaluated by TLC. Warming the reaction to room temperature did not change the outcome of the reaction. The reaction of *p*-methoxybenzaldehyde, *o*-methoxybenzaldehyde and benzaldehyde with **3** afforded the trimethylsilyl protected β -nitroalcohol along with the desired Henry reaction product **5**. The overall yield of a new carbon-carbon bond formation from the Mukaiyama nitro-aldol reaction for these three substrates is 34%, 74% and 64% respectively. All other examples using aromatic aldehydes afforded only β -nitroalcohol and the yields are stated in Table 2.

To try and understand this one pot procedure, the reaction with isovaleraldehyde was repeated, except during this attempt, TMSCl was not added to the reaction vessel. As expected, the reaction did not progress at all. Only recovered isovaleraldehyde was recovered from this reaction. Thus, the introduction of the in situ generated trimethylsilyl methylenenitronate was key for the Henry reaction to proceed in equimolar amounts with the aldehyde and substoichiometric amounts of scandium triflate.

Table 2. The Mukaiyama nitro-aldol of various aldehydes



Entry	R	Product	Rxn Time(h)	Yield(%)
1	(CH ₃) ₂ CHCH ₂	5a	20	68
2	t-Bu	5b	18	53
3	cyclohexyl	5c	72	32[55 ^a]
4	PhCH ₂ CH ₂	5d	72	55[85 ^a]
5	CH ₃ (CH ₂) ₃ CH ₂	5e	96	64
6	Et(CH ₃)CH	5f	72	25
7	<i>p</i> -O ₂ NC ₆ H ₄	5g	72	61[80 ^a]
8	<i>p</i> -FC ₆ H ₄	5h	96	77[99 ^a]
9	<i>p</i> -CH ₃ OC ₆ H ₄	5i	72	27 ^b [61 ^a]
10	<i>o</i> -CH ₃ OC ₆ H ₄	5j	72	26 ^c
11	<i>o</i> -NO ₂ C ₆ H ₄	5k	96	41[73 ^a]
12	furanyl	5l	120	40[48 ^a]
13	Ph	5m	72	44 ^d

^a yield is based on recovered aldehyde. ^b Isolated as an inseparable mixture of **5i** and the TMS protected nitroalcohol product. ^c this reaction produced 48% yield of the TMS ether protected nitroalcohol product. ^d this reaction produced 20% yield of the TMS ether protected nitroalcohol product.

3. Typical experimental conditions

Nitromethane (0.14 mL, 2.60 mmol) in anhydrous THF (10 mL) was cooled to -78°C and 1.6 M BuLi in Hexanes (1.63 mL, 2.60 mmol) was added. The reaction mixture was stirred for fifteen minutes. TMSCl (0.33 mL, 2.60 mmol) was then introduced and the reaction mixture was stirred for an additional fifteen minutes. Scandium(III) triflate (0.10 mmol) dissolved in THF (5 mL) was added to the mixture and immediately followed by the appropriate aldehyde (2 mmol). The reaction mixture was stirred at -78°C for 18–120 hours as indicated in Table 2 and the solvent was then removed under reduced pressure. Products were purified by flash chromatography (silica gel, 20% ethyl acetate/hexanes or 30% ethyl acetate/hexanes as eluent) to afford the β -nitroalcohol product. Each product was characterized by spectroscopic methods and the acquire data agreed with reported literature values (**5a**,²³ **5b**,²³ **5c**,²³ **5d**,²⁴ **5e**,²⁵ **5f**,²⁶ **5g**,²⁷ **5h**,²⁸ **5i**,²⁸ **5j**,²⁸ **5k**,²⁸ **5l**,²⁹ **5m**²⁸).

In conclusion, the first Mukaiyama nitro-aldol reaction with nitromethane as the starting nitroalkane is presented. Unlike previous examples, the reaction conditions are acidic and do not use an anhydrous fluoride source to promote the reaction, which is similar to the original conditions stated by Mukaiyama.¹⁷ This

reaction has been performed with equimolar amounts of nitronate and aldehyde, which could enable more elaborate nitronate molecules to be used in the Henry reactions. The diastereoselectivity of this reaction is presently being investigated.

Acknowledgments

The authors would like to acknowledge funding from the National Science and Engineering Council of Canada, Canadian Foundation of Innovation and Mount Saint Vincent University's Committee of Research and Publication that supported this work.

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Supplementary Material

Supplementary material (detailed experimental as well as the spectroscopic data for all compounds generated) have been provided with this letter.