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RING-OPENING OF NITROCYCLOPROPANES WITH AMINE AND PHENOL NUCLEOPHILES UNDER MICROWAVE IRRADIATION

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Abstract

The nucleophilic ring-opening reaction between nitrocyclopropane and amines or phenols was explored under microwave irradiation. These reactions have been conducted previously in the presence of a Lewis acid and under conventional heating at prolonged reaction times. By using microwave irradiation, the reaction time was significantly reduced for all substrates. A variety of functional groups were tolerated and yields were comparable to conventional heating methods in most cases. Additionally, the decarboxylation of a resultant product was also demonstrated under microwave conditions in a reduced reaction time.

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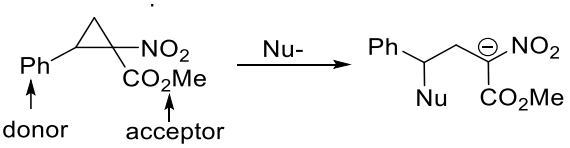
Introduction

Donor-acceptor (D-A) cyclopropanes have shown great utility as three carbon building blocks over the last few decades.[1] The ring strain of the cyclopropane paired with vicinally substituted donor and acceptor groups promote ring-opening reactions. However, nitrocyclopropane (NCP) carboxylates (**1**), a member of the D-A cyclopropane family, have not been used as frequently as their 1,1-diestercyclopropane counterparts, although the nitrogen moiety can be useful in constructing synthetically valuable compounds such as nitroalkenes and 1,2 amino alcohols.[2] Our group is exploring transformations of NCP carboxylates to increase the synthesis options available with these structures. We began by evaluating ring-opening reactions of nitrocyclopropanes with nucleophilic reagents (Scheme 1). The majority of the reported reactions of nitrocyclopropanes and nucleophiles require elevated temperatures or basic conditions that could lead to cyclopropane rearrangements and/or undesired by-products.[3] Organometallic reagents have been used to avoid these issues. However, heating under microwave conditions may be a suitable option to eliminate undesired reaction pathways by reducing the reaction time.

The Charette and Mattson groups have both investigated the ring-opening of NCP carboxylates and amines.[4-5] The Charette group initially demonstrated the thermal ring-opening of a nitrocyclopropane ring with aniline at 90 C in 17 hours. However, their subpar results with 2-bromoaniline, a more sterically hindered substrate, deterred them from pursuing the full scope of the thermal reaction and prompted the analysis of a Lewis acid ring-opening approach. They demonstrated that the Lewis acid, $Ni(ClO_4)_2 \times 6H_2O$, worked well with a range of amine derivatives although the reaction time was somewhat long at 17 hours. The Mattson group explored this transformation using boronate urea catalysts to activate the nitrocyclopropane. They successfully showed a range of substrates reacting with 10 mol% of catalyst in 48 hours. Both groups were able to demonstrate the synthetic utility of their approaches by further converting the initial products to medicinally relevant structures.[6-7] The Charette group also explored phenols as nucleophilic partners with nitrocyclopropanes in the presence of a base.[8] Unlike the amine substrates, the group was able to demonstrate a reasonable scope with NCPs under conventional heating. At 65 °C and 12 hours, 3-aryl-3-phenoxypropane products were accessed. The product scaffolds from amine and phenol substrates map onto several monoamine reuptake inhibitors (Figure 1).[6,9] Our group revisited thermal NCP activation using microwave irradiation. To our knowledge, microwave reactions involving NCPs have not been reported. In this instance they offer reduced reaction times and circumvent the need for a catalyst.



Scheme 1. General ring-opening of nitrocyclopropane with a nucleophile.

Materials and Methods

Microwave reactions were carried out using a CEM Discover microwave. Purification of reaction products was carried out by flash chromatography using Sorbtech 60 Å (40 - 63 µm) silica gel. Analytical thin layer chromatography (TLC) was performed on plastic-backed 250 µm layer silica plates visualized with either 254 or 365nm wavelengths. ^1H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were obtained on an Agilent 400MHz spectrometer using $CDCl_3$ as the solvent. All reactions were performed in 10 mL CEM microwave tubes. Solvents were used without purification and no considerations were made to exclude atmospheric moisture.

General Procedure A for the ring opening of nitrocyclopropane with amine derivatives.

A mixture of nitrocyclopropane **1** (100mg, 0.45 mmol), the desired amine (1.35 mmol, 3 equiv), and a stir bar was added to a

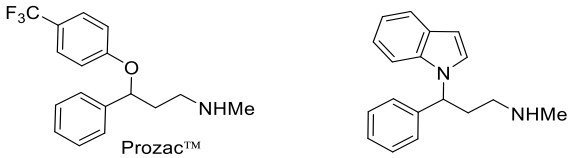


Figure 1. Examples of monamine reuptake inhibitors.

10 mL microwave vial with 2 mL of acetonitrile. The sealed tube was allowed to heat in the microwave with stirring at 90° Celsius for 3 hours at 150W. After the reaction was complete, the reaction mixture was transferred to a vial and the solvent was removed under reduced pressure to give the crude product. Column chromatography was performed with the specified solvent system to isolate the pure product.

General Procedure B for the ring opening of nitrocyclopropane with phenol derivatives.

A mixture of nitrocylopropane **1** (80mg, 0.36mmol), the desired phenol (3 equiv, 1.08mmol), and cesium carbonate (352 mg, 1.08mmol) was added to a clean microwave tube with a stir bar followed by acetonitrile (2 mL). The sealed tube was placed in the microwave and allowed to heat with stirring at 80° C for 1 hour at 150W. After the reaction was complete, the mixture was quenched with 5ml NH_4Cl (aq) and portioned between diethyl ether and water. The aqueous layer was extracted three times using 10ml of diethyl ether each time and the organic layers were combined. The organic layers were then washed with aqueous NaCl (brine) and dried over $MgSO_4$. The solution was filtered using gravity filtration and the solvent was removed with rotary evaporation. Column chromatography was performed with 100% benzene in most cases (Method 1). In cases where the residual phenol was difficult to remove, the solution was quenched with 5ml NH_4Cl (aq) and portioned between diethyl ether and water. The aqueous layer was extracted three times using 10ml of diethyl ether each time and organic layers were combined. The combined organic portion was then washed with 0.1M NaOH (5 mL) three times (Method 2). It was then dried over $MgSO_4$. The solution was filtered using gravity filtration and the solvent was removed with rotary evaporation. Purification by flash chromatography proceeded with 10% ethyl acetate/hexanes.

Methyl 4-anilino-2-nitro-4-phenylbutanoate (**3a**). The compound was prepared as in General Procedure A, except 2 equivalents of aniline was used in the reaction. The crude product was purified by column chromatography on silica gel (30% ethyl acetate/hexanes) to obtain **3a** as a yellow solid (72%, 1:1 dr). All spectral data match those previously reported.[10]

Methyl 4-[(4-methoxyphenyl)amino]-2-nitro-4-phenylbutanoate (**3b**). The compound was prepared as in General Procedure A. The crude product was purified by column chromatography on silica gel (30% ethyl acetate/hexanes) to obtain **3b** as a white solid (71%, 1:1 dr); All spectral data match those previously reported. [10]

Methyl 4-[(2-bromophenyl)amino]-2-nitro-4-phenylbutanoate (**3c**). The compound was prepared as in General Procedure A, except the reaction was run at 140 °C for 6 hours. The crude product was purified by column chromatography on silica gel (7% ethyl acetate/hexanes) to obtain **3c** as a yellow oil (91%, 1:1 dr). All spectral data match those previously reported. [10]

Methyl 2-nitro-4-phenyl-4-pyrrolidin-1-ylbutanoate (**3d**). The compound was prepared as in General Procedure A, but only 1.5 equivalents of piperidine was used. The crude product was purified by column chromatography on silica gel (5% MeOH in dichloromethane) to obtain **3d** as a beige solid (60%, 1:1 dr). All spectral data match those previously reported. [10]

Methyl 4-[(4-chlorophenyl)amino]-2-nitro-4-phenylbutanoate (**3e**). The compound was prepared as in General Procedure A, except the reaction was heated for 4 hours at 120 °C. The crude product was purified by column chromatography on silica gel (10% ethyl acetate/toluene) to obtain **3e** as a yellow oil (60 %, 1:1 dr). All spectral data match those previously reported. [10]

Methyl 4-[methyl(phenyl)amino]-2-nitro-4-phenylbutanoate (**3f**). The compound was prepared as in General Procedure A. The crude product was purified by column chromatography on silica gel (100% toluene) to obtain **3f** as a yellow oil (85 %, 1:1 dr). All spectral data match those previously reported. [10]

Methyl (4R)-4-(2,3-dihydro-1H-indol-1-yl)-2-nitro-4-phenylbutanoate (**3g**). The compound was prepared as in General Procedure A. The crude product was purified by column chromatography on silica gel (20% ethyl acetate/hexanes) to obtain **3g** as a beige solid (90 %, 1:1 dr. All spectral data match those previously reported. [10]

Methyl 2-nitro-4-phenoxy-4-phenylbutanoate (**5a**). The compound was prepared as in General Procedure B, Method A. The crude product was purified by column chromatography on silica gel (30% ethyl acetate/hexanes) to obtain **5a** as a yellow oil (65 %, 1:1 dr). All spectral data match those previously reported.[11]

Methyl 4-(4-methoxyphenoxy)-2-nitro-4-phenylbutanoate (**5b**). The compound was prepared as in General Procedure B, Method B. The crude product was purified by column chromatography on silica gel (30% ethyl acetate/hexanes) to obtain **5b** as a brown oil (38 %, 1:1 dr). All spectral data match those previously reported. [11]

Methyl 4-(3-chlorophenoxy)-2-nitro-4-phenylbutanoate (**5c**). The compound was prepared as in General Procedure B, Method A. The crude product was purified by column chromatography on silica gel (100% benzene) to obtain **5c** as a yellow oil (48 %, 1:1 dr). All spectral data match those previously reported. [11]

Methyl 4-{3-[(*tert*-butoxycarbonyl)amino]phenoxy}-2-nitro-4-phenylbutanoate (**5d**). The compound was prepared as in General Procedure B, Method A. The crude product was purified by column chromatography on silica gel (100% benzene) to obtain **5d** as a yellow oil (48 %, 1:1 dr). All spectral data match those previously reported. [11]

Methyl 2-nitro-4-phenyl-4-[4-trifluoromethyl)phenoxy]butanoate (**5e**). The compound was prepared as in General Procedure B, Method A except THF was used as the solvent. The crude product was purified by column chromatography on silica gel (100% benzene) to obtain **5e** as a yellow oil (62 %, 1:1 dr). All spectral data match those previously reported.[11]

Methyl 4-(1-napthyloxy)-2-nitro-4-phenylbutanoate (**5f**). The compound was prepared as in General Procedure B, Method A. The crude product was purified by column chromatography on silica gel (100% benzene) to obtain **5f** as a yellow oil (48 %, 1:1 dr). All spectral data match those previously reported.[11]

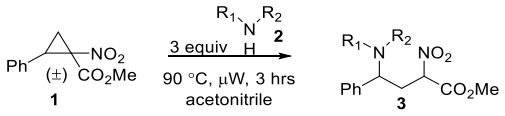
1-[3-nitro-1-phenylpropyl]indoline (**6**). Amine **3g** (80mg, 0.24

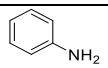
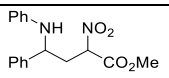
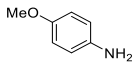
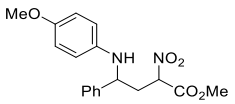
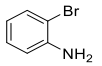
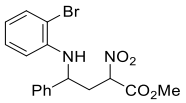
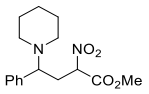
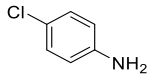
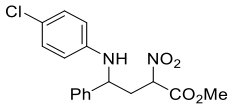
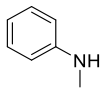
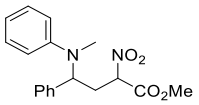
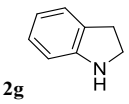
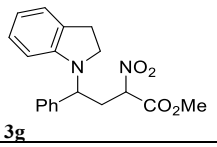
mmol) was added to a 10 mL microwave vial with dioxane (1 mL), water (.5 mL), and a stir bar. LiOH (5.6 mg (0.24 mmol) was added and the sealed tube was placed in the microwave at 150° Celsius for 30 minutes with stirring. The reaction contents were neutralized with 1M HCL and separated with ethyl acetate. The aqueous phase was extracted three times with EtOAc then the combined organic solutions were washed with saturated aqueous brine and dried over Na_2SO_4. Solvents were removed via rotary evaporation under reduced pressure and the crude product was purified by flash chromatography (20% EtOAc/Hex) to afford the pure product in 80% yield. All spectral data match those previously reported.[10]

Results and Discussion

Our initial work with NCP (**1**) and amines (**2**) in the microwave showed some evidence of conversion to product under the conditions employed by Charette at 90 °C in acetonitrile (Table 1). However, using 3 equivalents of the amine instead of 1.5 equivalents allowed the reaction to proceed in 3 hours compared to 17 hours of conventional heating. A variety of amines with different electronic and steric parameters worked well in the microwave although conditions were further optimized for some substrates.

Table 1. Ring opening of NCP by amine nucleophiles under microwave irradiation.



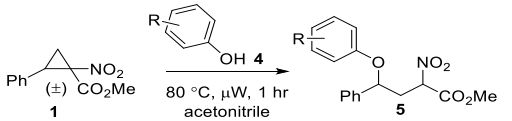
	amine	Product	Yield (%)
1	 **2a**	 **3a**	72[a]
2	 **2b**	 **3b**	71
3	 **2c**	 **3c**	91[b]
4	 **2d**	 **3d**	60[c]
5	 **2e**	 **3e**	60[d]
6	 **2f**	 **3f**	85
7	 **2g**	 **3g**	90

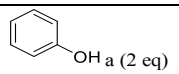
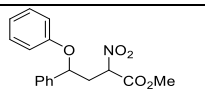
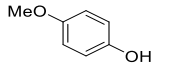
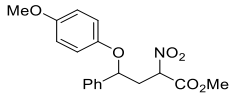
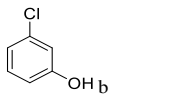
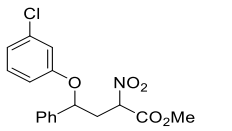
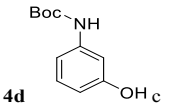
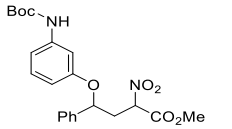
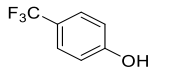
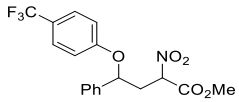
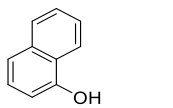
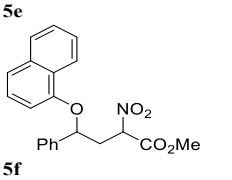
[a]Two equivalent of aniline used.[b]Reaction run at 140° C for 6 hours.
[c]1.5 equivalent of piperidine used. [d]Reaction run for 4 hours at 120° C.

The sterically hindered 2-bromoaniline proved to be a challenging substrate in this study, however, the reaction worked well at 140° C under 6 hours of microwave irradiation to give a 91% yield. In contrast, Charette reported a 15% yield under conventional heating for this substrate. The 91% yield in this case is also a testament to the lack of by-products seen under these conditions. The method is not as suitable for strongly electron withdrawing groups such as 4-nitroaniline. This substrate was also subjected to microwave heating for 6 hours at 150 °C, but nitrocyclopropane starting material remained after this time and heating for longer time periods or higher temps was not pursued to reach full conversion. Phenol nucleophiles were also attempted under microwave conditions to investigate the efficiency of these substrates with NCP (Table 2). These reactions were found to reach full conversion in an hour for all attempted substrates. The original conditions from the Charette work were optimized to use acetonitrile instead of THF. Unlike their amino counterparts, the yields for the corresponding products were poor to good. The substrate with the strongly electron withdrawing CF_3 substituent gave a yield of 29% in acetonitrile. However, the yield was improved to 62% by employing THF as the solvent for this substrate.

The mechanism for these transformations is believed to mimic those previously proposed in the literature where nucleophilic attack of the cyclopropane is followed by ring-opening and

Table 2. Ring opening of NCP by phenol nucleophiles under microwave radiation.



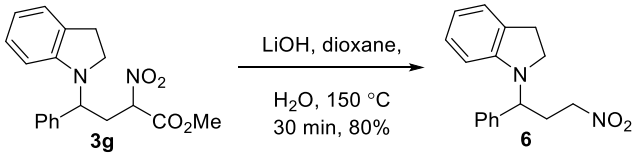
	phenol	product	Yield (%)
1	 **4a**	 **5a**	65
2	 **4b**	 **5b**	38
3	 **4c**	 **5c**	48
4	 **4d**	 **5d**	48
5	 **4e**	 **5e**	62[a]
6	 **4f**	 **5f**	48

[a]THF used as solvent.

protonation. As seen in previous work, the products were isolated as a ~1:1 mixture of diastereomers at the carbon bearing the electron withdrawing groups. For the amine, this process proceeded with no formation of by-products although Charette indicated that reactions above 90 °C produced the lactam product. However, the reaction time of 17 h may have contributed to the formation of this undesired product. The shorter reaction times may be responsible for the absence of the lactam.

After successfully obtaining the ring opened adducts, we explored further reactions using the 1,3-bifunctional product. One method of reducing the number of stereoisomers from this diastereomeric mixture is to perform a decarboxylation. This chemical manipulation also allows access to the scaffolds shown in **Figure 1**. The Charette group accessed a dual serotonin/norepinephnine reuptake inhibitor via an initial decarboxylation of an adduct such as **3g**. We observed that this decarboxylation step was also a time consuming reaction at 48 hours. We attempted to reduce the reaction time in this instance by utilizing microwave irradiation again. Decarboxylations are known to proceed under microwave conditions efficiently.[12] We were delighted to see product formation in 30 minutes using conditions that previously required 48 hours of heating at 80° C. This transformation proceeded with an 80 % isolated yield (Scheme 2).[10]

The successful coupling of nitrocyclopropanes with amine and phenol derivatives under microwave irradiation has been shown. This process proceeds in relatively short reaction times when compared to the current methods for accessing these substrates using a Lewis acid or conventional heating. Additionally, the expedient removal of the methyl ester via decarboxylation under microwave irradiation was demonstrated. Further work will explore other reactions of nitrocyclopropanes under microwave irradiation to increase efficiency in known reactions and promote novel reactions to create new structures.



Scheme 2. Decarboxylation of 1,3-bifunctional product under microwave irradiation.

Acknowledgment

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