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An unusual contra-Michael addition of $NaNO_2$–ceric ammonium nitrate to acrylic esters

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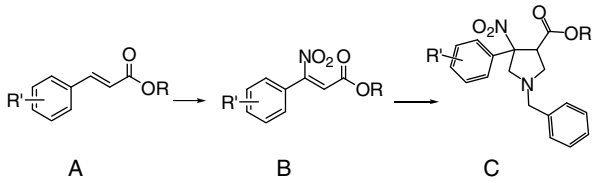
Abstract

This report describes a novel regioselective contra-Michael addition to cinnamic esters that utilizes $NaNO_2$–ceric ammonium nitrate.

Keywords: Contra-Michael addition; Anti-Michael addition; α-Nitro acrylic esters; Heteronuclear multiple-bond correlation NMR spectroscopy

The addition of nucleophilic reagents to α,β-unsaturated carbonyl moieties, the Michael reaction, leads to β-addition products.[1] Recently, Jayakanthan et al.[2] reported a hetero-Michael addition reaction for the preparation of β-nitro acrylic esters by utilizing $NaNO_2$–ceric ammonium nitrate ($NaNO_2$–CAN). Our original interest in this field was to synthesize compound C (Scheme 1), by the addition of a nitro-group to cinnamic ester A[2,3] followed by the [2+3] addition of *N*-benzyl-*N*-(methoxymethyl)-*N*-trimethylsilyl-methylamine to compound B.[4]

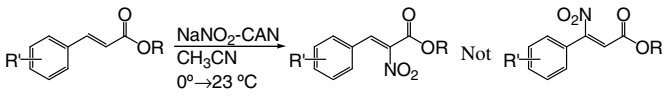
However, we failed to produce **C** by the sequence shown in Scheme 1, which prompted us to reexamine the regiochemistry of the putative β-nitro acrylic ester product **B**.[2,3] We have discovered that nitro-addition to cinnamic esters **A** did not follow the classical route, and that α-addition occurred exclusively (Scheme 2).



A B C

Scheme 1.

Nucleophilic addition to the α-position of α,β-unsaturated carbonyl compounds, contra-Michael addition, also widely termed anti-Michael addition, is a rare event.[5] Contra-Michael addition has been reported only for systems which have a strong electron-withdrawing group (EWG) in the β-position,[6] or from addition reactions mediated by a phosphine base,[7] palladium-based catalysis,[8] or organometallic reagents.[9] It is noteworthy that cinnamic esters do not have a strong EWG in β-position[10] and the reagent system $NaNO_2$–CAN is not known to favor contra-Michael addition.[2,3] Thus, to the best of our knowledge, this is the first example of an α-nitro addition to cinnamic esters by utilizing $NaNO_2$–CAN. The key to this discovery was a detailed structural analysis of the nitro-adducts obtained from the reaction. In previous publications describing nitro-adducts resulting from addition to



A D B

Scheme 2.

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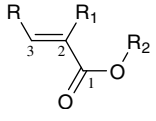
cinnamic esters,[2,3] the spectral characterization was incomplete and hence the regiochemistry of nitro addition was not correctly established. In this study, we present a detailed structural analysis of both α- and β-nitro adducts derived from cinnamic esters. This analysis was carried out with the help of heteronuclear multiple-bond correlation NMR spectroscopy (gHMBC).[11] This was essential as the reaction products possess only one olefinic proton, which renders other approaches, such as 1D proton and carbon NMR spectra, proton–proton *J*-coupling correlations and proton–proton NOE's analysis, inadequate.

The Jayakanthan et al.[2] report described the addition of the nitro-group to the following acrylic ester substrates (Table 1): ethylacrylate (**1**), methyl 2-butenoate (**2**), methyl 2-methylacrylate (**3**), ethyl cinnamate (**4**), methyl 3-(4-methylphenyl)acrylate (**5**), and methyl 3-(4-methoxyphenyl)-acrylate (**6**).

The adducts derived from esters **1-6** and $NaNO_2$–CAN, **1a**–**6a**, were analyzed by 1D proton and carbon NMR spectroscopy.[2] In adduct **1a**, the large proton–proton coupling between the H2 and the H3 olefinic protons (13.6 Hz) indicated vicinal positions of these protons consistent with β-nitro addition. Small proton–proton couplings between the olefinic proton and the methyl protons in adducts **2a** and **3a** (1.7 and 1.2 Hz, respectively) are consistent with four-bond couplings, and consequently with the assigned β-nitro acrylate regiochemistry. For adducts **4a**–**6a**, there are no available proton–proton couplings which would allow the assignment of regiochemistry, and carbon chemical shift data are also inconclusive. Therefore, the assigned β-nitro regiochemistry of these adducts was never confirmed.

Using the published procedure,[2,3] we have synthesized adduct **4a** and performed a comprehensive NMR analysis of the products.[12] In agreement with Jayakanthan's report,[2] the addition reaction of ethyl cinnamate with $NaNO_2$–CAN resulted in a mixture of two isomers in the ratio of 1:1.2. According to proton and carbon chemical shifts, the two isomeric adducts were identical to those previously reported.[2] Proton and carbon resonance assignments and structure elucidation of isomers **4a** were carried out by the analysis of 2D gCOSY, NOESY, gHSQC and gHMBC NMR spectra.[13] We have determined the regiochemistry of isomeric adducts **4a** by using multiple bond

Table 1



Compound	R	R_1	R_2
1	H	H	C_2H_5
2	CH_3	H	CH_3
3	H	CH_3	CH_3
4	Ph	H	C_2H_5
5	*p*-Tolyl	H	CH_3
6	*p*-Anisyl	H	CH_3

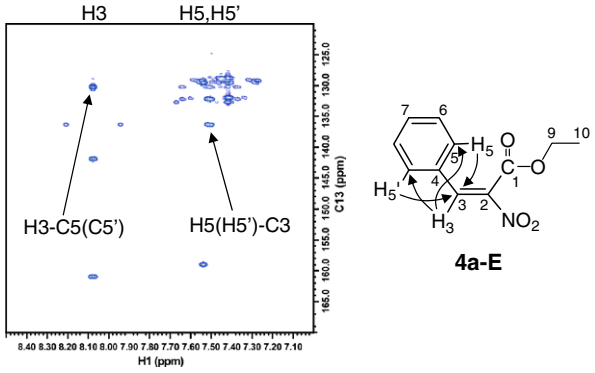


Fig. 1. Part of the gHMBC spectra of **4a-E** and **4a-Z**. The arrows point to the specific proton–carbon correlations which were used to assign the regiochemistry of **4a-E**.

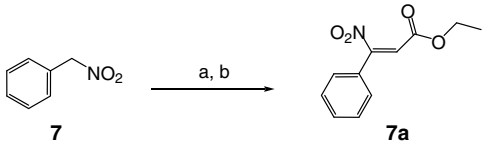
proton–carbon correlation gHMBC spectra (see Fig. 1 for **4a-E** isomer).

Cross-peaks of gHMBC spectra reveal correlations between proton and carbon nuclei separated by 2 and 3 sigma-bonds.[11] In gHMBC spectra of adducts **4a**, the correlations between the H3 proton and C5, C5′ carbons and between H5, H5′ protons and the C3 carbon were detected (see Fig. 1 for isomer **4a-E**). These correlations correspond to 3 bond separation between these pairs of nuclei and consequently to the β-position of the olefinic proton H3 and α-position of the nitro-group.

E and *Z* stereochemistry of adducts **4a** was established based on NOESY spectra. **4a-Z** isomer was assigned according to the NOE cross-peak between the H9 methylene protons of the ethyl group and the olefinic H3 proton. Concurrently, for **4a-E** isomer a NOE was detected between the H9 and H5(H5′) protons, and no NOE cross-peaks were found between the H3 and H9 protons.

In order to further prove that **4a** are α-adducts resulting from the addition of the nitro group to ethyl cinnamate, ethyl 3-nitro-3-phenylacrylate (**7a**) was synthesized from α-nitrotoluene (**7**) as shown in Scheme 3.[14,15]

Similar to the analysis of adducts **4a**, proton and carbon resonance assignment and structure elucidation of **7a-E** and **7a-Z** isomers were carried out by using 2D NOESY, gHSQC, and gHMBC NMR spectra. gHMBC spectra were primarily used to confirm the β-nitro regiochemistry of isomers **7a** (see Fig. 2 for isomer **7a-Z**). Thus, in gHMBC spectra, the cross peaks between the olefinic H2 proton and the C4 carbon and between H5, H5′ protons and the C3 carbon were readily found for both **7a-E** and



Scheme 3. Reagents and conditions: (a) 50% ethyl glyoxylate/toluene, Amberlyst-21, THF, 23 °C, 85% and (b) CH_3SO_2Cl, Et_3N, −20 °C, 76%.

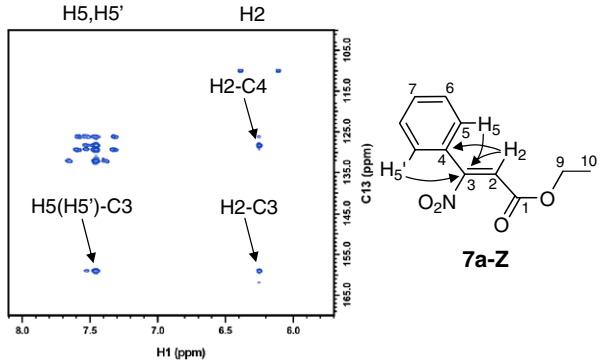


Fig. 2. Part of the gHMBC spectra of **7a-Z**. The arrows point to the specific proton–carbon correlations, which were used to assign the regiochemistry of **7a-Z**.

7a-Z isomers (see Fig. 2 for isomer **7a-Z**), which in turn confirmed the β-position of the nitro group.

E and Z stereochemistry of **7a** isomers was assigned by using NOESY spectra. **7a-Z** isomer revealed a cross-peak between the H2 and H5, H5′ protons, whereas no NOE cross-peaks between these protons were detected for **7a-E** isomer.

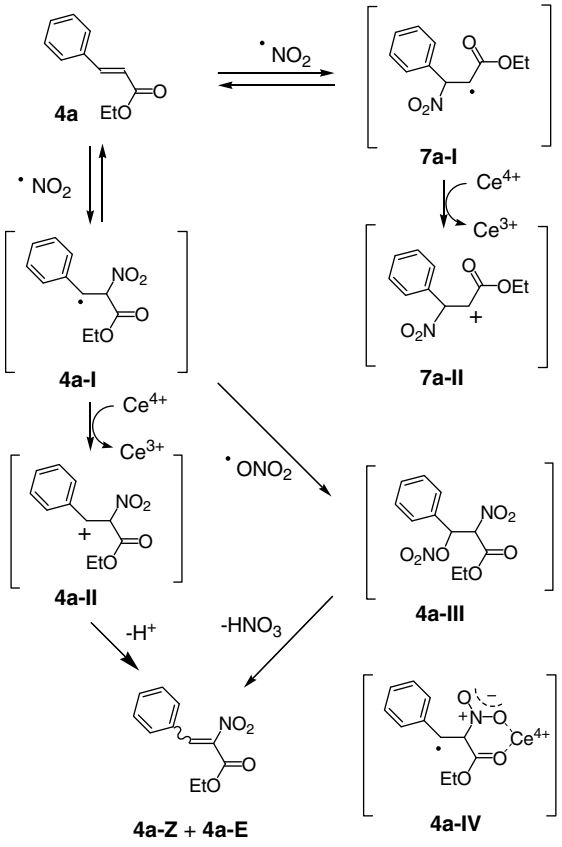
Proton and carbon chemical shifts of isomers **4a** and **7a** are summarized in Table 2. The largest difference in chemical shifts between α- and β-adducts was found for the carbon chemical shifts of the carbon atoms directly attached to the nitro group. Large positive α-effects of a highly electronegative nitro group in vinyl systems are well documented.[16] Combination of this effect and the positive α-effect of the phenyl group (+12 ppm)[16] resulted in a substantial low field shift of the C3 carbon chemical shift in the β-adducts, which becomes as large as 159 ppm (Table 2). This distinct feature of the carbon NMR spectra of β-nitro adducts of 3-phenyl (aryl) acrylic esters was applied to examine the structures of adducts **5a** and **6a** reported by Jayakanthan and coworkers.[2] Since only one carbon resonance with such large chemical shifts was found for these products (C1), we conclude that the regiochemistry of adducts **5a** and **6a** should be reassigned as the α-nitro adducts.

In summary, we have disclosed the first report of a novel contra-Michael addition to a cinnamic ester by utilizing $NaNO_2$–CAN. To explain this regiochemical outcome we propose the mechanism shown in Scheme 4. The reaction pathway leading to formation of the observed contra-Michael products **4a-E** and **4a-Z** is favored over the pathway leading to Michael adducts **7a-E** and **7a-Z** as a consequence of several possible factors. First, the phenyl group of intermediate **4a-I** can stabilize the adjacent radical and in addition would stabilize a potential carbocation intermediate **4a-II** resulting from oxidation of **4a-I** by Ce^{4+}. In contrast, carbocation **7a-II** resulting from the oxidation of **7a-I** would be energetically disfavored relative to **4a-II**. Furthermore, Ce^{4+} complexation to the ester and nitro functionalities as in the cyclic 6-membered ring intermediate **4a-IV** may also contribute to the stabilization of an intermediate with the radical center adjacent to the phenyl group. A 7-membered ring complex related to **7a-I** arising from delivery of the nitrite radical β to the ester functionality should be energetically less favored.[17] Finally, this discovery represents a simple, efficient method for the

Table 2
Proton and carbon NMR chemical shifts of **4a-Z**, **4a-E**, **7a-Z**, and **7a-E** adducts in $CDCl_3$, 25 °C[a]

Proton/carbon	4a-Z	4a-E	7a-Z	7a-E
H2	—	—	6.25	7.25
H3	7.54	8.08	—	—
H5, H5′	7.43	7.52	7.46	7.38
H6, H6′	7.43	7.46	7.46	7.47
H7	7.48	7.52	7.52	7.52
2-H9	4.38	4.45	4.25	4.12
3-H10	1.37	1.36	1.31	1.12
C1	159.15	161.11	161.90	163.18
C2	140.19	142.06	109.97	122.85
C3	132.84	136.49	159.05	159.45
C4	128.90	128.92	128.36	128.27
C5, C5′	129.67	130.39	126.20	129.91
C6, C6′	129.33	129.25	129.36	128.17
C7	132.10	132.32	132.14	130.69
C9	63.03	63.08	61.71	61.76
C10	13.99	13.67	13.81	13.68

[a] Data were recorded on Varian Inova 600 MHz spectrometer; chemical shifts are given in parts per million by referencing the signals of $CDCl_3$.



Scheme 4.

synthesis of dehydrophenylalanine derivatives, which as precursors of α-amino acids, are important synthetic intermediates.

Acknowledgment

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12. *Synthesis of* **4a-Z** *and* **4a-E**. To a round bottom flask were added ethyl cinnamate (1.00 g, 5.68 mmol) and anhydrous CH_3CN (50 ml). To the stirred solution cooled to 0 °C were slowly added $(NH_4)_2Ce(NO_3)_6$ (9.33 g, 17.0 mmol) and $NaNO_2$ (1.70 g, 17.0 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 22 h, then filtered through Celite and the filter pad was washed with CH_3CN (2 × 50 ml). The combined filtrate and washings were poured into cold water (100 ml), extracted with CH_2Cl_2 (3 × 50 ml), dried over Na_2SO_4, filtered, and concentrated. The residue was separated by silica gel flash chromatography (EtOAc/hexane, 0–25%; AnaLogix IntelliFlash 280) to afford **4a-Z** and **4a-E** (ratio: ~1:1) in 40% yield as a slightly yellow oil. Compound **4a-Z**: ^{1}H NMR ($CDCl_3$, 600 MHz), δ 7.54 (1H, s, H3), 7.48 (1H, m, H7), 7.43 (4H, m, H5, H5′, H6 and H6′), 4.38 (2H, q, $J = 7.1$ Hz, H9), 1.37 (3H, t, $J = 7.1$ Hz, H10); ^{13}C NMR ($CDCl_3$, 150 MHz), δ 159.15 (C1), 140.19 (C2), 132.84 (C3), 132.10 (C7), 129.67 (C5 and C5′), 129.33 (C6 and C6′), 128.90 (C4), 63.03 (C9), 13.99 (C10). Compound **4a-E**: ^{1}H NMR ($CDCl_3$, 600 MHz), δ 8.08 (1H, s, H3), 7.52 (3H, m, H5, H5′ and H7), 7.46 (2H, m, H6 and H6′), 4.45 (2H, q, $J = 7.1$ Hz, H9), 1.36 (3H, t, $J = 7.1$ Hz, H10); ^{13}C NMR ($CDCl_3$, 150 MHz), δ 161.11 (C1), 142.06 (C2), 136.49 (C3), 132.32 (C7), 130.39 (C5 and C5′), 129.25 (C6 and C6′), 128.92 (C4), 63.08 (C9), 13.67 (C10).
13. *NMR spectroscopy*: NMR spectra were acquired at 25 °C on a Varian Unity-Inova 600 MHz spectrometer equipped with 3 mm inverse detection probe and pulsed field gradient. Samples were prepared in $CDCl_3$ in concentration 10–20 mg/ml. Compounds **4a-Z** and **4a-E** were studied as a mixture. 2D gCOSY experiments were performed in a magnitude mode with gradient selection method. 512 points in t1 and 3600 complex points in t2 were acquired. 2 scans per each t1 point with 1 s delay between scans were used. The spectral width was 7200 Hz in both dimensions. 2D NOESY experiments were performed in a phase sensitive method. 512 complex points in t1 and 3600 complex points in t2 were acquired. 8 scans per each t1 point with 0.5 s mixing time and 1.5 s delay between scans were used. The spectral width was 7200 Hz in both dimensions. 2D ^{1}H–^{13}C gHSQC experiments were performed in a phase sensitive mode with gradient selection method. 256 complex points in t1 (^{13}C) and 2108 complex points in t2 (^{1}H) were acquired. 8 scans per each t1 point with 1 s delay between scans were used. The spectral width was 26,000 (or 4000) Hz in t1 and 7200 Hz in t2 dimension. The t1 dimension included linear prediction to 512 complex points. 2D ^{1}H–^{13}C gHMBC experiments were performed in a magnitude mode with gradient selection method. 800 points in t1 (^{13}C) and 2552 complex points in t2 (^{1}H) were acquired. 16 scans per each t1 point with 1.5 s delay between scans were used. The spectral width was 29,996 Hz t1 and 7200 Hz in t2 dimension. For all 2D experiments zero-filling and a sine-bell window function were applied prior to Fourier transformation.
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15. *Synthesis of* **7a-Z** *and* **7a-E**: To a round bottom flask were added nitromethyl benzene (3.93 g, 28.6 mmol), 50% ethyl glyoxylate/toluene (6.20 ml, 31.5 mmol), Amberlyst-21 (2.00 g), and THF (20 ml). The reaction mixture was stirred at rt for 18 h, filtered, and concentrated in vacuo. The crude product was carried over to next step without further purification (5.79 g, 85%). To a solution of the crude product from the previous step (1.29 g, 5.41 mmol) in CH_2Cl_2 (20 ml) cooled to −20 °C were added CH_3SO_2Cl (1.30 ml, 16.2 mmol) and Et_3N (2.30 ml, 16.2 mmol). The reaction mixture was allowed to warm to room temperature, stirred overnight, then poured into H_2O, and extracted with CH_2Cl_2 (3 × 100 ml). The organic layer was dried over $NaSO_4$, filtered, and concentrated. The residue was separated by silica gel chromatography (EtOAc/hexane 0–20%; AnaLogix Intelli-Flash 280) to afford **7a-Z** (237 mg, 20%) as a clear yellow oil and **7a-E** (676 mg, 56%) as a white solid. Compound **7a-Z**: ^{1}H NMR ($CDCl_3$, 600 MHz), δ 7.52 (1H, m, H7), 7.46 (4H, m, H5, H5′, H6 and H6′), 6.25 (1H, s, H2), 4.25 (2H, q, $J = 7.1$ Hz, H9), 1.31 (3H, t, $J = 7.1$ Hz, H10); ^{13}C NMR ($CDCl_3$, 150 MHz), δ 161.90 (C1), 159.05 (C3), 132.14 (C7), 129.36 (C6 and C6′), 128.36 (C4), 126.20 (C5 and C5′), 109.97 (C2), 61.71 (C9), 13.81 (C10). Compound **7a-E**: ^{1}H NMR ($CDCl_3$, 600 MHz), δ 7.50 (1H, m, H7), 7.47 (2H, m, H6 and H6′), 7.38 (2H, m, H6 and H6′), 7.25 (1H, s, H2), 4.12 (2H, q, $J = 7.1$ Hz, H9), 1.12 (3H, t, $J = 7.1$ Hz, H10); ^{13}C NMR ($CDCl_3$, 150 MHz), δ 163.18 (C1), 159.45 (C3), 130.69 (C7), 129.91 (C5 and C5′), 128.27 (C4), 128.17 (C6 and C6′), 122.85 (C2), 61.76 (C9), 13.68 (C10).
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