Highly Stereoselective Nitration of Chalcone Derivatives with Nitric Oxide

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Abstract: A novel nitration of chalcone derivatives with nitric oxide affords *E*- α -nitropropenones exclusively in good yield. The reaction is most likely initiated by electrophilic addition of nitric dioxide to the C=C double bond at the α -position.

Key words: stereoselective, nitration, chalcone, nitric oxide, *E*-2nitropropenone

Introduction of nitrogen-containing functional groups into organic compounds is one of the important subjects in synthetic organic chemistry.¹ There has been much effort invested in discovering new methods to effect this transformation, among them, the nitration of olefins is a facile method for C-N bond formation. Although great progress has been made in this field, the α -vinylic nitration of α , β unsaturated systems has not been well documented so far. It is particularly noteworthy that the α -vinylic nitration of α , β -unsaturated systems has elicited wide interest. The resulting α -nitrochalcones are important intermediates in organic synthesis because of their activated C=C double bond and their adjacent nitro and carbonyl groups.² Dorrow³ reported that the condensation of *N*-benzalbutylamine with ω -nitroacetophenone afforded α -nitrochalcone in 48% yield. Later, Lehnert modified this procedure using titanium tetrachloride in anhydrous tetrahydrofuran, for the condensation of aromatic aldehydes with ω -nitroacetophenone at a lower temperature, afforded α-nitrochalcones in 76% yield.^{2a,4} Yet, these methods have suffered from one or more of the following drawbacks: harsh conditions, expensive reagents, multi-step preparation of materials, or unsatisfactory yield. As part of our ongoing research program on the chemistry of nitric oxide (NO), reactions of NO with arylhydrazones,⁵ epoxides,⁶ aziridines,7 and Wittig reagent 8 were studied. Our interests in NO have prompted us to perform the nitration of chalcone derivatives with NO. In this communication, we will report a novel approach to α -nitrochalcones.

In a typical experiment,⁹ the reaction of chalcone derivative **1** with NO was carried out at ambient temperature, which was initiated by nitric dioxide (NO₂), and gave the single mono-nitration product, *E*-2-nitropropenone (**2**), with yields ranging from 73% to 90% (Table 1). Spectral data (¹H and ¹³C NMR, MS, HRMS, IR,⁹ 1D NOE, HMQC, and HMBC) obtained for **2** indicated that the geometry of **2** was well controlled. The nitro group was located exclusively at the α -position with respect to the carbonyl group of *E*-configured chalcone derivates (Scheme 1).^{2,10}



Scheme 1

It is well known that NO is a highly stable free radical. It neither abstracts a hydrogen atom nor adds to an unactivated double bond, but it can couple with other radicals. NO₂ is appreciably more reactive than NO and reacts preferentially with dienes.¹¹ In the present case, a trace of oxygen oxidizes NO to NO₂, then electrophilic addition of NO₂ to the double bond of the chalcone derivative occurs selectively at the α -position with respect to its carbonyl group to give a carbon-centered radical 3 (Scheme 2). Coupling of NO with the β -carbon of **3** takes place affording nitroso compound 4. Addition of two equivalents of NO to the nitroso group of 4 gives an *N*-nitroso-*N*-nitrite 5^{11} which rearranges to diazonium nitrate 6. Finally, the intermediate 6 undergoes anti-elimination to give the final product 2. No reaction occurred when the system was completely protected from air. Attempted nitration of chalcones with NO₂ led to very complicated reaction mixtures. Therefore, a trace of oxygen is considered to initiate the reaction via NO₂. At the very beginning of the reaction, oxygen oxidizes NO to NO₂, which then initiates the reaction. Once the reaction is initiated, the NO₂ required afterward comes from the reaction of NO with HNO₃,¹¹ which is produced during the elimination (Scheme 2), rather than from NO and O₂. An excess of NO₂ will react with the intermediates to give many byproducts.¹² Actually, the coupling of NO with the intermediate 3 is diastereoselective because both possible diastereomers may be stable. The formation of the E-2-nitropropenone, exclusively, is most likely attributed to the energetically favorable anti-elimination and the higher stability¹⁰ of the *E*-isomer with respect to the *Z*-isomer.

The results listed in Table 1 seem to indicate roughly that an electron-donating substituent at the *para*-position of the phenyl ring (R) in $\mathbf{1}$ leads to a higher yield as can be seen for $\mathbf{1d}$ and $\mathbf{1e}$. It may be attributed to the electron-

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donating group stabilizing the radical **3** through resonance. Neither the substituents on the phenyl ring ($\mathbf{R'}$) nor the replacement of the aryl group with an alkyl group have any obvious effects on the chemical yields, as shown in the cases of **1b**, **1c**, and **1h**. This is reasonable when you consider the large distance between $\mathbf{R'}$ and the radical center of the intermediate **3**.

Table 1 Reaction of Chalcone Derivatives with NO at AmbientTemperature in $CH_2Cl_2^a$

Entry	1	R	R′	2	Yield (%) ^t
1	1a	Ph	Ph	2a	78
2	1b	Ph	p-FC ₆ H ₄	2b	75
3	1c	Ph	p-BrC ₆ H ₄	2c	76
4	1d	<i>p</i> -MeC ₆ H ₄	Ph	2d	89
5	1e	<i>p</i> -MeC ₆ H ₄	<i>p</i> -OMeC ₆ H ₄	2e	90
6	1f	<i>p</i> -MeC ₆ H ₄	p-ClC ₆ H ₄	2f	82
7	1g	<i>p</i> -OMeC ₆ H ₄	p-BrC ₆ H ₄	2g	73
8	1h	Ph	Me	2h	80

^a All reaction times were 15 h.

^b Isolated yields after column chromatography.

We have presented a new approach for preparing α -nitro chalcone derivatives directly from chalcone derivatives using NO. The main advantages of this methodology are its high steroselectivity, readily available starting materials, and convenient performance under mild conditions. We are currently working on extending the scope of the reaction by broadening both the range of substrates and nitrogen sources.

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- Typical Procedure A stock solution was prepared by (9) dissolving 1a (104 mg, 0.5 mmol) in anhyd CH₂Cl₂ (100 mL). NO was produced by the reaction of a 1 M H₂SO₄ solution with a sat. aq solution of NaNO₂ under an argon atmosphere (H₂SO₄ was added dropwise). NO was carried by argon and purified by passing it through a series of scrubbing bottles containing distilled water, 4 M NaOH, and CaCl₂ (in this order; bottles were kept under an argon atmosphere). Purified NO was bubbled through the stock solution, which was previously degassed with argon for 6 min. In the course of degassing, the argon flow rate was controlled by regulating the flow-meter at 0.8 Lmin⁻¹ and the stock solution was kept at a pressure of up to +10 mm (water column over local atmospheric pressure at 10 °C). The total amount of NO was passed through the solution estimated to be roughly 300 mmol at local atmospheric pressure using the ideal gas law. After completion of the reaction, as indicated by TLC, the reaction mixture was dried over anhyd MgSO₄, concentrated under vacuum, and purified by column chromatography on silica gel (200–300 mesh, EtOAc-PE), giving pure 2a (98 mg, 78%); mp 92 °C. IR (KBr): 3062, 2923, 1679, 1638, 1522, 1316, 1231, 947, 765, 687 cm⁻¹ ¹H NMR (300 MHz, CDCl₃): δ = 7.35 (m, 2 H), 7.42 (m, 3 H), 7.49 (m, 2 H), 7.63 (m, 1 H), 7.96 (m, 2 H), 8.34 (s, 1 H). ¹³C NMR (75 MHz, CDCl₃): δ = 128.9, 129.2 (2 C), 129.3, 131.0, 132.3, 133.5, 134.9, 137.3, 144.7, 188.2. MS-EI: *m*/*z* = 253 (M⁺), 191, 132, 105, 102, 77, 63. HRMS-ESI: *m*/*z* calcd for C₁₅H₁₂NO₃: 254.0812; found: 254.0811.
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