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α-Nitro Ketone Synthesis Using *N*-Acylbenzotriazoles

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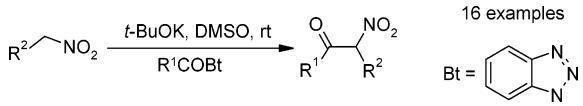

Readily available *N*-acylbenzotriazoles **2a**−**l** (derived from a variety of aliphatic, (hetero)aromatic, and *N*-protected α-amino carboxylic acids) smoothly convert primary **3a**−**c** and α-functionalized primary nitroalkanes **3d** into the corresponding α-nitro ketones **5a**−**p** in yields of 39−86% (average 63%).

Introduction

Over the years, α-nitro ketones have gained much attention due to their great versatility.[1] The juxtaposition of the carbonyl carbon and the carbon bearing the nitro group offers flexible reactivity patterns that are particular to this class of compound providing viable and often superior means to various functionalized materials.[2] α-Nitro ketone intermediates are extensively utilized for the syntheses of diverse classes of compounds, including oxazolidinones,[3] isoxazoles,[4] pyrroles,[5] furoxans,[6] amides,[7] ketones,[1a,8] α-deuterated ketones,[1a,9] α-aminoketones,[10] and tosyl hydrazones.[1a]

Recent interest in α-nitro ketones has been directed toward their reductive conversion into diastereomerically enriched vicinal nitro alcohols.[11] The nitro group in these versatile building blocks can readily be reduced with retention of configuration,[12] and the resulting amino alcohols are key intermediates in the construction of numerous pharmacologically important compounds[3,13] and chiral auxiliaries.[14] Additionally, α-nitro ketones are valuable precursors for the syntheses of many classes of natural products including jasmonoids and prostaglandin intermediates[1a] and pheromones.[15]

Available methods for the synthesis of α-nitro ketones include four main approaches (Scheme 1): (i) nitrations of (a) enol acetates with trifluoroacetic anhydride and ammonium nitrate,[16] (b) potassium enolates with pentyl nitrate,[17] or (c) enol silyl ethers with tetranitromethane;[18] (ii) oxidations of (a) olefins using trimethylsilyl nitrate−chromium trioxide[19] or (b) β-nitrostyrenes using lithium *tert*-butyl peroxide;[20] (iii) Henry reactions followed by

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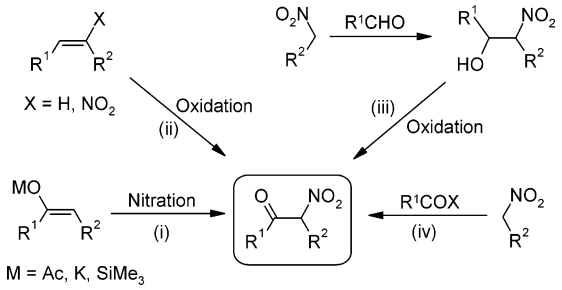
SCHEME 1



oxidation using (a) pyridinium chlorochromate,[21] (b) aluminachromium(VI) oxide,[22] or (c) $K_2Cr_2O_7$;[23] and (iv) C-acylation of nitro compounds.

Approaches of type (iv) are the most frequently employed: nitroalkanes are treated with activated derivatives of acids, especially acyl cyanides,[24] acid anhydrides,[25] esters,[25]and *N*-acylimidazoles.[26] In the last method, the reagent is prepared in situ either from the carboxylic acid and 1,1′-carbonyldiimidazole or from the acyl halide and 2 equiv of imidazole. A shortfall of the acyl cyanide method to nitroalkanes[24] is the apparent restriction to acetylation and benzoylation; the yields of α-nitro ketones having substitution at the α-position range from 26 to 53% (average 40%). Literature examples using carboxylate esters for the condensation are generally restricted to the use of nitromethane;[26a] in some cases, the use of the acylimidazole requires harsh dilithioanions[26b] prepared under inert atmosphere to provide the acylated products (23−92%, average 58%), and these conditions might limit its use as a general method.

N-Acylbenzotriazoles show great potential in organic synthesis as activated derivatives of carboxylic acids: they are effective for the *N*-acylation of amines to give amides,[27] the *O*-acylation of aldehydes to provide esters,[28] and the *C*-acylation of ketones,[29] sulfones,[30] and nitriles[31] affording *β*-diketones, *β*-keto sulfones, and *β*-keto nitriles, respectively. In continuation of our work, we now report a simple and efficient procedure that allows the preparation of aliphatic and (hetero)aromatic α-nitro ketones **5a**−**p** in yields of 39−86% by the *C*-acylation of a variety of primary nitroalkanes.

Results and Discussion

N-Acylbenzotriazoles **2a**−**l** were readily prepared from benzotriazole and the corresponding carboxylic acid in excellent yields according to a recent procedure.[32] Nitroalkanes **3a**−**d** were treated with 2 molar equiv of *t*-BuOK in dimethyl sulfoxide at 10 °C. Subsequent addition of *N*-acylbenzotriazoles **2a**−**j** afforded the desired aliphatic, aromatic, and heteroaromatic α-nitro ketones **5a**−**m** in yields of 48−86% (average 67%) (Scheme 2 and Table 1). This synthetic route improved the previously reported[26a] yields of **5d** (32%) and **5e** (72%) to 81% and 83%, respectively. The yields of previously unreported α-nitro ketones **5b**,**f**−**m** were 57−86%. The modest 48% yield of the product **5c** may reflect the decrease in the electrophilicity of the acyl group by conjugation with the triple bond.

Further generalization of this approach by applying this methodology to *N*-acylbenzotriazoles **2k,l**, derived from *N*-protected amino acids allowed the synthesis of the previously unreported category of α-nitro ketones **5n**−**p** in 39−71% isolated yields (Scheme 2 and Table 1).

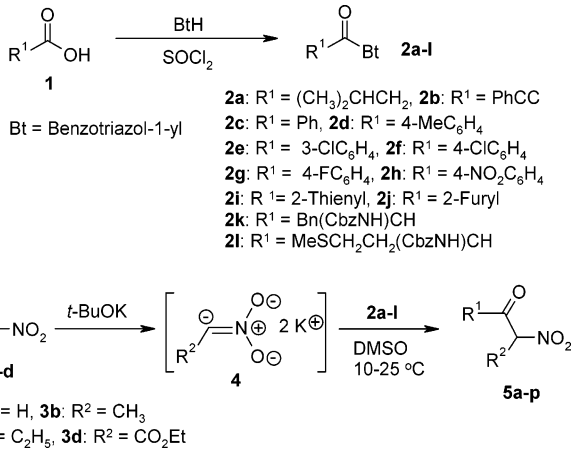
Elemental analyses and NMR spectral data support the structural assignments of **5a**−**p**. The ^{1}H NMR spectra of the α-nitro ketones **5a**−**p** reveal a characteristic signal in the region 5.28−6.57 ppm, which is unambiguously assigned to the proton attached to a carbon between the carbonyl and nitro groups. ^{13}C NMR spectra of com-

TABLE 1. Preparation of α-Nitro Ketones 5a−p

compd	R^1 of R^1COBt **2**	R^2 of $R^2CH_2NO_2$ **3**	yield (%)
5a	$(CH_3)_2CHCH_2$	H	83
5b	$(CH_3)_2CHCH_2$	CO_2Et	72
5c	PhC≡C	H	48
5d	Ph	H	81[a]
5e	3-ClC_6H_4	H	83[b]
5f	4-ClC_6H_4	CH_3	62
5g	4-$CH_3C_6H_4$	CH_3CH_2	57
5h	4-ClC_6H_4	CH_3CH_2	73
5i	4-FC_6H_4	CH_3CH_2	76
5j	4-$NO_2C_6H_4$	CH_3CH_2	78
5k	2-thienyl	H	85
5l	2-furyl	H	79
5m	2-furyl	CH_3CH_2	86
5n	Bn(CbzNH)CH	H	59
5o	Bn(CbzNH)CH	CH_3	39
5p	$CH_3S(CH_2CH_2(CbzNH)CH$	H	71

[a] Lit.[26a] yield 32%. [b] Lit.[26a] yield 72%.

SCHEME 2[a]



[a] For designation of R^1 and R^2 in **5** see Table 1.

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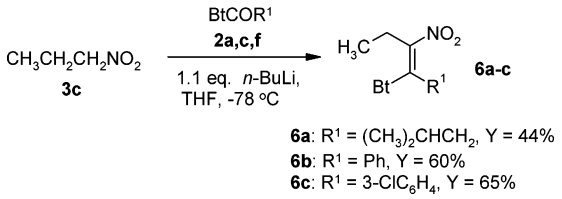
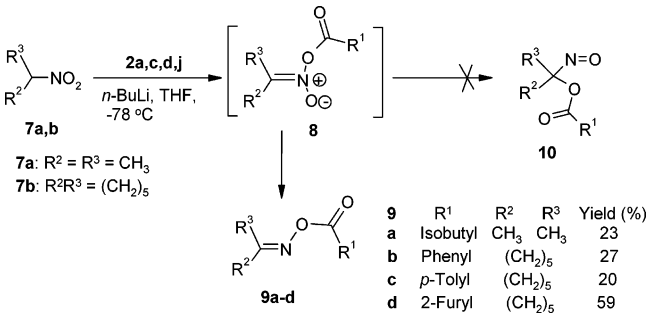
SCHEME 3



SCHEME 4



9	R^1	R^2	R^3	Yield (%)
a	Isobutyl	CH_3	CH_3	23
b	Phenyl	$(CH_2)_5$		27
c	*p*-Tolyl	$(CH_2)_5$		20
d	2-Furyl	$(CH_2)_5$		59

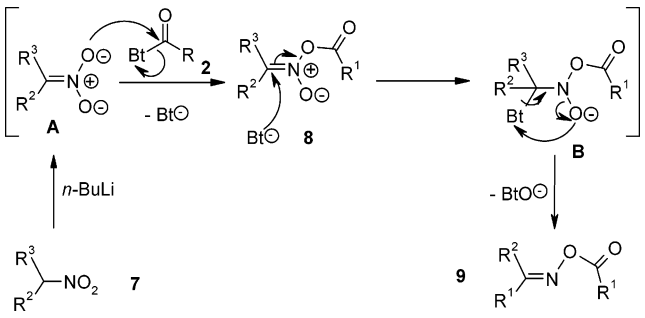
pounds **5a**−**p** clearly show a signal for the carbonyl group in the region 172.0−195.9 ppm.

Acylation of primary nitroalkanes **3** with *N*-acylbenzotriazoles **2** was studied under a variety of conditions. The reaction using sodium hydride, Et_3N, or *t*-BuOK in tetrahydrofuran (THF) at room temperature gave no product; however, in the case using *n*-BuLi in THF at −78 °C, the reaction provided the condensation product of type **6** in 44−65% yields instead of the acylated product of type **5** (Scheme 3). The *E*-configuration of the double bond was indicated by NOE experiments: for example, irradiation of the methylene protons of the isobutyl moiety of **6a** at 2.47 ppm showed no NOE effects on the methylene protons of the ethyl group at 3.45 ppm. Spectroscopic data together with elemental analyses support the structures of **6a**−**c**. In addition to the characteristic signals of the benzotriazolyl group, the ^{13}C NMR spectra clearly show the newly formed olefinic bond of **6a**−**c** as signals in the region δ = 161.8−162.7 ppm and 163.0−169.2 ppm; signals for the carbonyl group and the carbon flanked between nitro and carbonyl groups were absent.

The reactions of primary nitroalkanes with *N*-acylbenzotriazoles **2** required 2 molar equiv of base for the best yields. The reactions of nitromethane with **2c** and **2e** were examined in the presence of 1 and 2 molar equiv of base. The use of 1 molar equiv of *t*-BuOK provided the acylated products **5d** and **5e** in 32% and 37% yields; however, the use of 2 molar equiv dramatically enhanced the yields to 81% and 83%, respectively. Apparently, the use of 2 molar equiv of base allows formation of the doubly metalated complex of type **4** causing *C*-acylation to occur in preference to *O*-acylation, thus providing high yields of *C*-acylated products.

Rather surprisingly, reactions of the secondary nitroalkanes, 2-nitropropane (**7a**), and nitrocyclohexane (**7b**) with *N*-acylbenzotriazoles **2a**,**c**,**d**,**j** in the presence of 1.3 molar equiv of *n*-BuLi in THF at −78 °C afforded *O*-acyl oximes **9a**−**d** in 20−59% isolated yields (Scheme 4). The structures of the products were established by NMR spectral data as that of the *O*-acyl oximes **9** instead of products of type **5** or the rearranged products of type **10**

SCHEME 5



as previously reported.[33] The *O*-acylated products **9a**−**d** with the acyl group attached to oxygen are evidenced by ^{13}C NMR spectra which show relatively upfield signals of the carbonyl groups in the region 169.3−170.3 ppm relative to α-nitro ketones **5**. Moreover, in addition to the expected signals in the aromatic region there is an extra carbon at 156.6−164.3 ppm that is definitively assignable to the sp^2 carbon attached to nitrogen of the *O*-acylated products **9**. Furthermore, an APT experiment for **9d** confirmed the absence of the expected quaternary carbon attached to carbonyl and nitro as in the *C*-acylated products **5** or nitroso as in **10** that rules out these possible structural assignments. The structures of **9a**−**d** were definitively confirmed by determination of the single-crystal X-ray structure of **9d** (crystallographic data for **9d** are included in the Supporting Information).

A plausible mechanism for the formation of **9a**−**d** is depicted in Scheme 5. The nitronates **A**, generated from secondary nitroalkane **7** under basic conditions, attacks *N*-acylbenzotriazole **2** to nitronic anhydride intermediate **8** and benzotriazolide anion (Bt^-). A possible counterattack by Bt^- on the electrophilic carbon center in **8** to form addition adduct **B**, and subsequent 1,2-*syn*-elimination to afford *O*-acyl oxime **9** and 1-hydroxybenzotriazole salt (BtOLi) is speculative.

Although the nitroalkanes successfully *C*-acylated are limited to primary examples, our synthetic procedure for the preparation of α-nitro ketones is advantageous compared with previously known methods. It utilitizes readily available and stable starting materials and gives high yields. It has demonstrated good generality since *N*-acylbenzotriazoles can be derived from either aliphatic, (hetero)aromatic, or *N*-protected α-amino carboxylic acids providing a very large variety of α-nitro ketones.

In summary, a simple, efficient, and broadly applicable synthetic methodology for the preparation of α-nitro ketones has been developed by the *C*-acylation of primary nitroalkanes with *N*-acylbenzotriazoles. In addition, the reaction of *N*-acylbenzotriazoles with secondary nitroalkanes opens a new way to *O*-acyl oximes. The easy accessibility of *N*-acylbenzotriazoles from the corresponding carboxylic acid and the simple workup gives the approaches substantial utility.

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Experimental Section

4-Methyl-1-nitro-2-pentanone (5a). Nitromethane (**3a**) (0.122 g, 2 mmol) was reacted with 1-benzotriazole-1-yl-3-methylbutan-1-one (**2a**) (0.406 g, 2 mmol) according to the general procedure. Purification by column chromatography (eluent: hexanes/EtOAc, 10:1) gave 0.241 g (83%) as a colorless oil: ^{1}H NMR δ 5.28 (s, 2H), 2.43 (d, J = 6.9 Hz, 2H), 2.27−2.13 (m, 1H), 0.98 (d, J = 6.9 Hz, 6H); ^{13}C NMR δ 195.8, 83.5, 49.0, 24.4, 22.2. Anal. Calcd for $C_6H_{11}NO_3$: C, 49.65; H, 7.64; N, 9.65. Found: C 50.07; H, 7.85; N, 9.75.

1-[(*E*)-6-Methyl-3-nitrohept-3-en-4-yl]-1*H*-benzotriazole (6a). 1-Nitropropane (**3c**) (0.178 g, 2 mmol) was reacted with 1-benzotriazole-1-yl-3-methylbutan-1-one (**2a**) (0.406 g, 2 mmol) according to the general procedure. Purification by column chromatography (eluent: hexanes/EtOAc, 10:1 then 5:1) gave 0.241 g (44%) as a colorless oil: ^{1}H NMR δ 8.49 (d, J = 8.4 Hz, 1H), 8.11 (d, J = 8.2 Hz, 1H), 7.66 (t, J = 7.8, Hz, 1H), 7.49 (t, J = 8.0 Hz, 1H), 3.46 (q, J = 7.6 Hz, 2H), 2.47 (d, J = 7.0 Hz, 2H), 2.27 (septet, J = 6.6 Hz, 1H), 1.42 (t, J = 7.6 Hz, 3H), 1.09 (d, J = 6.6 Hz, 6H); ^{13}C NMR δ 169.2, 161.8, 146.3, 130.7, 129.8, 125.6, 119.7, 115.4, 41.6, 25.7, 22.3, 20.6, 11.1. Anal. Calcd for $C_{14}H_{18}N_4O_2$: N, 20.42. Found: N, 20.62.

3-Methyl-1-{[(1-methylethylidene)amino]oxy}-1-oxobutane (9a). 2-Nitropropane (**7a**) (0.534 g, 6 mmol) was reacted with 1-benzotriazole-1-yl-3-methylbutan-1-one (**2a**) (0.812 g, 4 mmol) according to the general procedure. Purification by column chromatography (eluent: hexanes/EtOAc, 19:1) gave 0.145 g (23%) as a colorless oil: ^{1}H NMR δ 2.29 (d, J = 6.9 Hz, 2H), 2.24−2.13 (m, 1H), 2.06 (s, 3H), 2.00 (s, 3H), 1.00 (d, J = 6.5 Hz, 6H); ^{13}C NMR δ 170.3, 163.6, 41.9, 25.7, 22.3, 21.9, 16.9. Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.05; H, 9.93; N, 9.17.

Supporting Information Available: Procedures, experimental details, and structural data for all new compounds not described in the text. The Cambridge database number for the crystallographic data for compound **9d** (Figure 1) is CCDC 269102. This material is available free of charge via the Internet at http://pubs.acs.org.

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