Allylic Amidation of Olefins by Ene Reaction of Acylnitroso Compounds Generated in situ by Oxidation of Hydroxamic Acids

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A one-pot allylic amidation procedure, which employs the ene reaction of acylnitroso compounds **2** with electron-rich olefins **3a,b**, is presented; the acylnitroso enophile is generated in situ by oxidation of hydroxamic acids **1** with iodosobenzene diacetate. The resulting *N*-allylhydroxamic acids **4** (ene products) are quantitatively acetylated for ease of handling; as an example, the reduction of the acetylated derivative **5b** by samarium diiodide was carried out to afford the *N*-allyl amide **6b** in quantitative yields.

Introduction

Allylic amines are versatile building blocks, as exemplified in the preparation of α- and β-amino acids,[1] alkaloids,[2] and carbohydrate derivatives.[3] A variety of methods have been developed in the last few decades for the direct allylic amination of olefins.[4] The ene reaction of azo enophiles with alkenes[5] diethyl azodicarboxylate (DEAD) and triazolindiones (TAD) have been intensively employed] constitutes a mild and convenient method. Another class of potentially useful nitrogen enophiles are the nitroso compounds, but in view of their labile nature they have been used relatively little for this purpose. For example, acylnitroso compounds, the so-called "super(di)enophiles", need to be generated in situ because of their low persistence; a result of their high electrophilic reactivity.[6]

In this context, Kirby et al.[7][8] and Keck et al.[9] generated acylnitroso intermediates by thermal retrocleavage of their Diels−Alder adducts with 9,10-dimethylanthracene or cyclopentadiene in the presence of various olefins, and has demonstrated their propensity to undergo an ene reaction. Alternatively, the in-situ oxidation of nitrile oxides by *N*-methylmorpholine *N*-oxide has led to intermediary acylnitroso compounds, which afford ene products with olefins in high yields.[10] Unfortunately, in both methods, the precursors are cumbersome to prepare and the olefin partner for the ene reaction must be used in high excess.

Clearly a convenient and efficient method for the in-situ generation of acylnitroso enophiles is required, and one which utilizes readily available starting materials, e.g., the selective oxidation of hydroxamic acids. Such an approach has been documented for the hetero [4+2] cycloaddition;[7−11] however, for the ene reaction, poor yields have been obtained.[9] This work reports a viable synthetic methodology (Scheme 1) and demonstrates that good yields of the intermediary acylnitroso can be achieved under mild conditions, as manifested by the ene reaction with the appropriate olefins. The ready availability of the hydroxamic acids, the mild conditions of the oxidation, and the convenient workup all combine to provide a promising direct allylic amidation of olefins.

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Results and Discussion

An extensive investigation showed that iodosobenzene and iodosobenzene diacetate are best suited as oxidizing agents for the mild and clean in-situ preparation of the desired acylnitroso compounds (trapped as ene products with tetramethylethylene) from commercially available hydroxamic acids. While the mild oxidants iodine and 2,3-dichloro-4,5-dicyanobenzoquinone (DDQ) were ineffective in oxidizing the benzylhydroxamic acid (**1b**), in the case of lead tetraacetate, tetraethylammonium periodate,[12] and the Dess−Martin reagent, complex side reactions with low yields (ca. 20%) of the ene product were observed.

For iodosobenzene diacetate, as well as iodosobenzene, the simple one-pot procedure with only 3 equiv. of the olefin afforded *N*-allylhydroxamic acids as ene products. This is illustrated for the three olefins **3a−c** and the five hydroxamic acids **1a−e** in Scheme 1. For ease of handling, the more labile *N*-allylhydroxamic acids **5** were quantitatively acetylated to the more persistent *O*-acetylated derivatives **6** (Scheme 1).[13]

The product data shown in Table 1 demonstrate that the more electron-rich the olefin, the higher the yield of the ene product. For the tetramethylethylene (**3a**), the yields are high (60−90%) for all hydroxamic acids **1a−e**. Thus, the electronic nature of the acyl functionality of the hydroxamic acid, i.e., alkyl (**1a**,**b**) versus aryl (**1c−e**), and the *para* substituent for the latter, i.e., *p*-NO_2 (**1c**) versus *p*-MeO (**1e**), matters little to the efficacy of the ene reaction of the in-situ generated *N*-acylnitroso enophile with a reactive olefin such as tetramethylethylene. In contrast, the less electron-rich 2-methylbutene (**3b**) with the most reactive *p*-nitro-substituted hydroxamic acid **1c** gave the corresponding acetylated ene product in a yield of only 54%; one regioisomer was exclusively observed. For methyl tiglate (**3c**), an elec-

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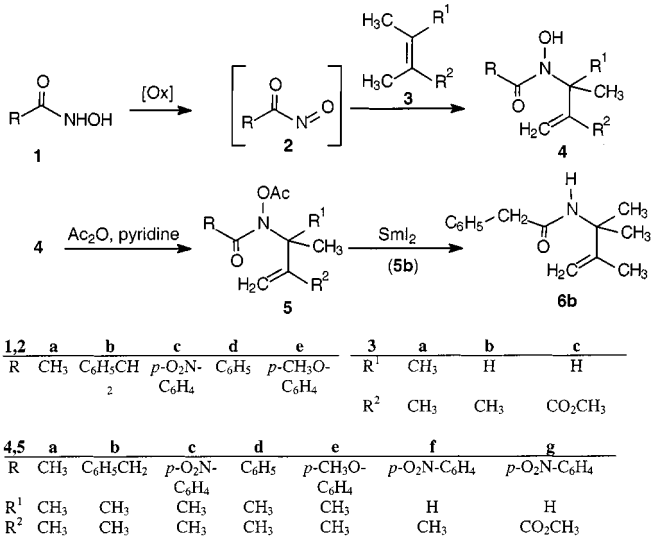

Scheme 1. Oxidative in-situ generation of *N*-acylnitroso enophiles from hydroxamic acids and their ene reaction with olefins

tron-poor ene substrate, only 10% of the acetylated ene adduct **5g** was isolated, even when the most reactive hydroxamic acid **1c** was employed. Moreover, the hydroxamic acid **1d** and its *p*-nitro-substituted derivative **1c** did not afford any ene product with cyclohexene and the terminal olefin 2-methyl-1-octene. For these sluggishly reacting olefins, the labile acylnitroso enophile decomposes mainly into *p*-nitrobenzoic anhydride, a competitive side reaction.

Table 1. Yields of nitroso ene products

Entry	Hydroxamic acid[a]	Olefin	Product	Yield (%)[b]
1	**1a**		**5a**	62
2	**1b**		**5b**	87
3	**1c**	**3a**	**5c**	82
4	**1d**		**5d**	70
5	**1e**		**5e**	70
6	**1c**	**3b**	**5f**	54
7	**1c**	**3c**	**5g**	10[c]

[a] A solution of the hydroxamic acid in CH_2Cl_2/DMF (10:1) was slowly added to a solution of iodosobenzene diacetate (1.1 equiv.) and the olefin (3 equiv.) in dichloromethane at 0°C. – [b] Isolated material by silica-gel chromatography. – [c] Main product in this case is the *p*-nitrobenzoic anhydride.

A synthetically useful direct allylic aza functionalization according to Scheme 1 requires that the hydroxamic acid ene adduct is readily reduced to the desired amino functionality. With the *O*-acetylated derivative **5b** as a model substrate, a variety of common reducing agents (Al/Hg, $LiAlH_4$, Zn/HCl)[14] proved to be problematic in converting the N–O to the N–H bond, as reported. However SmI_2[15] (Scheme 1) served as selective reductant and the **5b** → **6b** transformation was achieved quantitatively.

The one-pot process, namely the in-situ oxidation of hydroxamic acids in the presence of olefins, represents a useful and convenient allylic amidation from common and commercially available starting materials. For electron-rich olefins, high yields of allylic amides are obtained, which are versatile building blocks in natural product chemistry.

Experimental Section

General: IR: Perkin–Elmer Model 1605 FT-IR Spectrophotometer. – ^{1}H NMR (250 MHz): Bruker AC 250 ($CHCl_3$, at δ = 7.26 as internal standard). – ^{13}C NMR (63 MHz): Bruker AC 250 ($CHCl_3$, at δ = 77.0 as internal standard). – MS: Finnigan Mat 8200. – Exact mass: Finnigan Mat MAT90. – M.p.s: Büchi B-545 (uncorrected values). – Column chromatography was performed on silica gel (32–63 μm mesh Merck).

General Procedure for the Nitroso Ene Reaction: Hydroxamic acid (1.3 mmol), dissolved in CH_2Cl_2/DMF (10:1, 25 mL) was added over a period of 8 h to a solution of the olefin (4.0 mmol) and iodosobenzene diacetate (1.5 mmol) in CH_2Cl_2 (25 mL) at 0°C. The reaction mixture was stirred for another 16 h, treated with satd. sodium thiosulfate solution (25 mL), the organic phase dried with $MgSO_4$, and the solvent removed (20°C, 7.5 Torr). Acetic anhydride (5 mL) and pyridine (1 mL) were added to the crude product and the mixture stirred for 30 min at 20°C. The product was purified by azeotropic distillation with toluene (3 × 50 mL, 50°C) followed by column chromatography (petroleum ether/Et_2O, 8:1).

Ene Adduct 5a: 62%, colorless needles, m.p. 28–30°C. – IR (KBr): $\tilde{\nu}$ = 3095 cm^{-1}, 2990, 2930, 2855, 1800 (C=O), 1685 (C=O), 1375, 1170, 890, 860. – ^{1}H NMR: δ = 1.32 (s, 3 H), 1.45 (s, 3 H), 1.72 (s, 3 H), 1.90 (s, 3 H), 2.12 (s, 3 H), 4.76 (s, 1 H, C=CH_2), 4.85 (s, 1 H, C=CH_2). – ^{13}C NMR: δ = 19.8, 20.8, 23.9, 26.0, 27.7, 68.4, 111.3, 150.4, 170.8 (C=O), 172.8 (C=O). – $C_{10}H_{17}NO_3$ (199.3): calcd. C 60.28, H 8.60, N 7.06; found C 60.29, H 8.69, N 7.08.

Ene Adduct 5b: 87%, colorless needles, m.p. 98–101°C. – IR (KBr): $\tilde{\nu}$ = 3070 cm^{-1}, 2980, 2925, 2880, 1750 (C=O), 1670 (C=O), 1370, 1240, 895. – ^{1}H NMR: δ = 1.31 (s, 3 H), δ = 1.34 (s, 3 H), 1.71 (s, 3 H), δ = 2.12 (s, 3 H), 3.44 (s, 1 H, benzylic H), δ = 3.46 (s, 1 H), 4.73 (s, 1 H, C=CH_2), 4.83 (s, 1 H, C=CH_2), 7.09–7.26 (m, 5 H, aryl H). – ^{13}C NMR: δ = 17.9, 18.8, 23.8, 25.6, 41.0, 67.0, 109.9, 127.1, 128.7, 129.7, 134.2, 149.1, 169.9, 172.2. – $C_{16}H_{21}NO_3$ (275.4): calcd. C 69.79, H 7.69, N 5.09; found C 69.42, H 7.30, N 5.06.

Ene Adduct 5c: 82%, colorless powder, m.p. 56–58°C. – IR (KBr): $\tilde{\nu}$ = 3075 cm^{-1}, 2990, 2940, 2865, 1800 (C=O), 1655 (C=O), 1525, 1350, 1165, 895, 845. – ^{1}H NMR: δ = 1.51 (br s, 3 H), 1.62 (br s, 3 H), 1.82 (s, 3 H), 1.90 (s, 3 H), 4.90 (s, 1 H, C=CH_2), 5.01 (s, 1 H, C=CH_2), 7.60 (d, ^3J = 9.0 Hz, 2 H, aryl H), 8.18 (d, ^3J = 9.0 Hz, 2 H, aryl H). – ^{13}C NMR: δ = 17.5, 18.8, 24.3, 25.0, 67.7, 111.0, 123.4 (2 ×), 128.3 (2 ×), 142.1, 148.1, 148.8, 169.0 (C=O), 169.5 (C=O). – $C_{15}H_{18}N_2O_5$ (306.3): calcd. C 58.82, H 5.92, N 9.15; found C 58.77, H 5.89, N 9.06.

Ene Adduct 5d: 70%, colorless needles, m.p. 53–55°C. – IR (KBr): $\tilde{\nu}$ = 3095 cm^{-1}, 2990, 2930, 2880, 1795 (C=O), 1655 (C=O), 1380, 1175, 890. – ^{1}H NMR: δ = 1.48 (s, 3 H), 1.62 (s, 3 H), 1.78 (s, 3 H), 1.91 (s, 3 H), 4.88 (s, 1 H, C=CH_2), 5.00 (s, 1 H, C=CH_2), 7.30–7.47 (m, 5 H, aryl H). – ^{13}C NMR: δ = 18.0, 19.3, 24.7, 25.7, 67.3, 110.2, 127.0, 127.9 (2 ×), 130.1 (2 ×), 135.9, 148.5, 169.3 (C=O), 169.5 (C=O). – $C_{15}H_{19}NO_3$ (261.3): calcd. C 68.94, H 7.33, N 5.36; found C 69.30, H 7.11, N 5.23.

Ene Adduct 5e: 70%, colorless liquid. – IR (neat): $\tilde{\nu}$ = 3095 cm^{-1}, 2990, 2840, 2560, 1795 (C=O), 1660 (C=O), 1360, 1170, 910, 840. – ^{1}H NMR: δ = 1.62 (br s, 6 H), 1.92 (s, 3 H), 1.96 (s, 3 H), 3.87

(s, 3 H, OCH_3), 4.92 (s, 1 H, C=CH_2), 5.05 (s, 1 H, C=CH_2), 6.87 (d, ^3J = 8.85 Hz, 2 H, aryl H), 7.56 (d, ^3J = 9.15 Hz, 2 H, aryl H). − ^{13}C NMR: δ = 18.0, 19.2, 25.2 (2 ×), 55.1, 67.0, 109.9, 113.0 (2 ×), 127.8, 129.1 (2 ×), 148.6, 161.0, 169.2 (C=O), 170.2 (C=O). − $C_{16}H_{21}NO_4$ (291.3): calcd. C 65.96, H 7.27, N 4.81; found C 65.74, H 7.24, N 4.68.

Ene Adduct 5f: 54%, colorless liquid. − IR (neat): ṽ = 3110 cm^{-1}, 2985, 2940, 2850, 1800 (C=O), 1660 (C=O), 1525, 1350, 1180, 940, 912, 850. − ^{1}H NMR: δ = 1.38 (d, ^3J = 6.72 Hz, 3 H, CHCH_3), 1.83 (s, 3 H), 1.98 (s, 3 H), 4.94−5.05 (m, 3 H), 7.72 (d, ^3J = 8.85 Hz, 2 H, aryl H), 8.24 (d, ^3J = 9.00 Hz, 2 H, aryl H). − ^{13}C NMR: δ = 15.0, 17.6, 20.6, 58.4, 114.0, 123.6 (2 ×), 128.8 (2 ×), 140.7, 143.2, 149.3, 168.2 (C=O), 168.6 (C=O). − $C_{14}H_{16}N_2O_5$ (292.3): calcd. C 57.53, H 5.52, N 9.58; found C 57.62, H 5.31, N 9.27.

Ene Adduct 5g: 10%, colorless liquid. − ^{1}H NMR: δ = 1.39 (d, ^3J = 7.02 Hz, 3 H), 1.96 (s, 3 H), 3.72 (s, 3 H), 5.25−5.48 (m, 1 H), 5.82 (s, 1 H, C=CH_2), 6.37 (s, 1 H, C=CH_2), 7.72 (d, ^3J = 8.54 Hz, 2 H), 8.20 (d, ^3J = 8.85 Hz). − ^{13}C NMR: δ = 15.8, 18.0, 52.3, 54.3, 123.5 (2 ×), 127.6, 128.7 (2 ×), 137.9, 140.1, 148.9, 165.8 (C=O), 167.1 (C=O), 167.9 (C=O). − $C_{15}H_{16}N_2O_7$ (336.1): calcd. C 53.57, H 4.80, N 8.33; found C 53.27, H, 4.82, N 8.28.

Reduction of the Ene Adduct 5b: 104 mg (0.38 mmol) of the ene adduct **5b** was dissolved in THF (3 mL). A 0.1 M solution of SmI_2 in THF was added under argon until the reaction mixture remained greenish blue (ca. 10 mL). After stirring for 15 min at 20°C, the solution was treated with water (20 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The organic phases were combined, dried with $MgSO_4$, and the solvent removed (20°C, 7.5 mbar) to afford 80.2 mg (97%) of the amide **6b** as colorless needles, m.p. 102−104°C. − IR (KBr): ṽ = 3315 cm^{-1} (NH), 3265 (NH), 3065, 2970, 2930, 2875, 1655 (C=O), 1550, 1260, 890. − ^{1}H NMR: δ = 1.30 [s, 6 H, C(CH_3)$_2$], 1.58 (s, 3 H), 3.45 (s, 2 H, PhCH_2), 4.72−4.74 (m, 2 H, C=CH_2), 5.22 (br. s, 1 H, N*H*), 7.16−7.26 (m, 5 H, aryl H). − ^{13}C NMR: δ = 18.9, 26.9 (2 ×), 44.8, 56.5, 109.9, 127.2, 129.0 (2 ×), 129.3 (2 ×), 135.3, 148.8, 169.8 (C=O). − MS (EI); *m*/*z* (%): 218 [M$^+$+1] (4), 217 [M$^+$] (17), 174 (9), 126 (19), 100 (5), 92 (8), 91 (40), 84 (45), 83 (100), 82 (14), 67 (16), 65 (16), 58 (26), 55 (65). − Exact mass for $C_{14}H_{19}NO$: calcd. 217.1467, found 217.1466.

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