Transition Metal Catalyzed Oxidation, 10[◇]

Zirconium-Catalyzed Oxidation of Primary Aliphatic Amines to Nitro Compounds with *tert*-Butyl Hydroperoxide

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Primary aliphatic amines are oxidized with *tert*-butyl hydroperoxide to the corresponding nitro compounds in 50−98% yield using $Zr(Ot\text{-}Bu)_4$ as the catalyst. The CH-acidic nitro compounds are not epimerized under these reaction conditions.

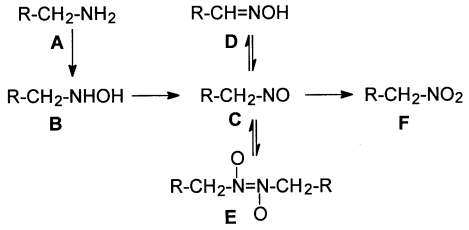
In a previous communication we have demonstrated the ability of the system $Zr(Ot\text{-}Bu)_4$/*tert*-butyl hydroperoxide (TBHP)/molecular sieves to oxidize primary aromatic amines effectively to the aromatic nitro compounds.[1] The yields were generally very high in spite of the occurrence of two reaction intermediates (e.g. hydroxylamines and nitroso compounds) demonstrating the powerful oxygen transfer capability of the zirconium alkoxide/TBHP reagent. This successful oxygenation of the *aromatic* amines prompted us to investigate the reactivity of primary *aliphatic* amines in presence of this catalytic oxidation system.

Aliphatic nitro compounds are the starting materials for a number of interesting transformations (for reviews see ref.[2][3]). A very valuable reaction is for example the conversion of primary and secondary nitroalkanes into aldehydes or ketones (Nef reaction).[4][5] The importance of aliphatic nitro compounds in organic synthesis is further underlined by the recently published method for conversion into carboxylic acids.[7] The strong electron-withdrawing property of the nitro group is exploited in CC bond-forming reactions with carbonyl compounds such as the Henry reaction.[6] On the other hand, the nitro group is also a good leaving group in substitution reactions.[8]

The usual procedure for the preparation of aliphatic nitro compounds is the nucleophilic substitution of unhindered alkyl bromides or iodides with the nitrite ion (review[9]). However, the ambident character of the nitrite anion normally leads to substantial amounts of the corresponding nitrous acid ester. The yield of the nitro compounds is increased by reaction in very polar aprotic solvents such as DMF and by use of the expensive silver nitrite (Victor Meyer reaction).[9] The oxidation of the corresponding primary amines which are easily prepared by substitution reactions from alkyl tosylates or alkyl halides also affords the nitro compounds. Various reagents such as ozone,[10] $NaMnO_4$,[11] $KMnO_4$,[12] peracetic acid,[13] *meta*-chloroperbenzoic acid (MCPBA),[14][15a] and dimethyldioxirane[16][17] were used for this oxidation. However, catalytic procedures with environmentally safe oxidants such as hydrogen peroxide[15b] or alkyl hydroperoxides such as *tert*-butyl hydroperoxide are still required.

The oxidation of primary amines **A** proceeds via a number of intermediates[18] (Scheme 1) and an efficient oxidant is required for rapid conversion to the target nitro compounds **F**. The occurrence of hydroxylamines **B** in the oxidation of aromatic amines was established indirectly by the isolation of azoxy compounds which were formed by coupling with nitroso compounds **C**.[1] The aromatic nitroso compounds were isolated in ca. 50% yield in the case of donator-substituted anilines.[1] Further difficulties in the aliphatic series may arise from the tautomerization of the nitroso compounds **C** to the corresponding oximes **D** or dimerization to **E**.[18] Incomplete oxidation was sometimes observed in the reaction with MCPBA caused by the formation of nitroso dimers **E**.[14]

Scheme 1



A variety of primary amines shown in Scheme 2 with different steric hindrance and functionalities have been

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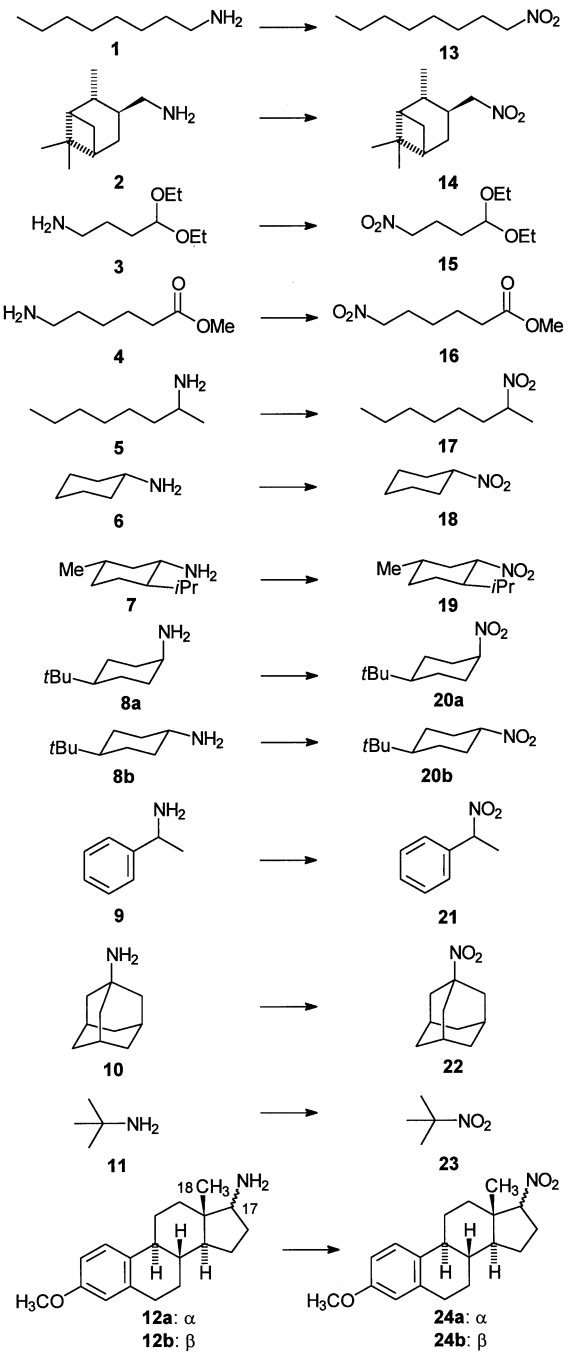
selected to test the scope and limitation of the zirconium alkoxide/TBHP oxygenation procedure. The isolated yields of the oxidation of the amines **1**−**12** to the corresponding nitro compounds **13**−**24** are listed in Table 1 and refer to analytically pure samples. The slightly yellow-colored crude aliphatic nitro compounds are easily purified by filtration through a short silica-gel column followed by crystallization or destillation under reduced pressure.

Scheme 2



Amino groups attached to primary and secondary carbons (Table 1, entries 1−4 and 5−8) are oxidized in comparable yields (65−94%). A nearly quantitative yield was obtained with 1-adamantyl amine (**10**, entry 10, NH_2 on a tertiary center) whereas some losses occurred during workup of the volatile 2-methyl-2-nitropropane (**11**, 64%, entry 11). It is noteworthy that functional groups such as acetals or esters are not affected using catalytic amounts of the zirconium catalyst (entries 3 and 4). The lowest yields (50%, entry 9) are obtained with benzylic amines. The reaction time with sterically hindered substrates such as (−)-menthylamine (**7**)[23] increases the reaction time only slightly and the yield of the nitro compound **19** is even increased compared to less sterically hindered amines (94%, entry 7). Equatorial or axial amino groups present in the *cis*- and *trans*-4-*tert*-butylcyclohexylamines **8a** and **8b** are oxidized to the corresponding nitro compounds **20a** and **20b** with comparable rates as shown by kinetic experiments. This observation is in contrast to the oxidation of the corresponding axial and equatorial 4-*tert*-butylcyclohexanols which show remarkable differences in the reaction rate in the oxidation to 4-*tert*-butylcyclohexanone with the same catalytic system reflecting the different reaction type (e.g. dehydrogenation of the alcohols versus oxygenation of the amines).[27]

Table 1. Oxidation of various primary amines with the system Zr(O*t*-Bu)$_4$/*tert*-butyl hydroperoxide (TBHP)/molecular sieves

entry	amine	product	time [h]	yield [%]	b. p. [°C]/ *p* [Torr]	ref; (b.p.) [°C]/ *p* [Torr]
1	**1**	**13**	5	72	47/0.1	[19] (60/1)
2	**2**	**14**	5	81	79−80/0.3	–
3	**3**	**15**	1.5	70	60/0.2	–
4	**4**	**16**	1	65	78−80/0.2	[20] (196/1)
5	**5**	**17**	5	84	42−43/0.2	[21] (61/1)
6	**6**	**18**	5	82	32/0.2	[22] (79/10)
7	**7**	**19**	8	94	73−74/0.3	[23] (93−94/3)
8	**8a/8b**	**20a/20b**	5	80	72−78/0.6	[24] (70−90/0.4)
9	**9**	**21**	6	50	82−83/1.0	[25] (75−76/0.7)
10	**10**	**22**	6	98	m.p. 158	[17] m.p. 159
11	**11**	**23**	5	64	125−127/760	[26] (127/760)
12	**12a/12b**	**24a/24b**	5	50	**24b**: m.p. 169−170	–

Furthermore, no epimerization of the less stable *cis* compound **20a** to the thermodynamically more stable *trans* derivative **20b** was observed during the reaction time (5 h, continuous GC control). This result was confirmed by the oxidation of (+)-*iso*-menthylamine to the corresponding nitro compound (not shown) and also in the oxidation of the 17α- and 17β-aminoestron methyl ethers **12a/12b**. The retention of stereochemistry during the oxidation is of great preparative importance and increases the value of this catalytic oxidation method.

Finally, we have tested the method on the more complex 17α- and 17β-aminoestron methyl ethers **12a/12b**. The amines[28] were prepared by reduction of the corresponding oxime with sodium in ethanol[29] yielding a 1:7 mixture of the α- and β-amines **12a** and **12b** as confirmed by analysis of the ^{1}H-NMR spectra of the corresponding acetamides. The application of the oxidation method on **12a/12b** gave a mixture of the corresponding nitro compounds **24a** and **24b** (entry 12, 50% yield after chromatography). The α/β-ratio remained unchanged as indicated by the lowfield signals for

17-H at δ = 4.5 (β isomer **24b**) and 4.7 (α isomer **24a**). The major β isomer **24b** was easily purified by crystallization and the axial β position of the nitro group was unequivocally established by the absence of *trans*-diaxial relationships of 17-H with the neighboring methylene protons in the ^{1}H-NMR spectrum. In addition, proton 17-H of the α isomer **24a** shows a distinct NOE effect with the neighboring methyl group (C-18).

Careful analysis of the GC and ^{1}H-NMR spectra in the oxidation of the amino group on primary (entries 1−4) and benzylic positions (entry 9) revealed the occurrence of small amounts of the corresponding aldehydes or acetophenone (5−21%). Evidently, oxidative cleavage of the nitro compounds occurred to some extent with these sterically unhindered substrates.[6] Accordingly, the yields were somewhat lower compared to the sterically more hindered amino group on secondary or tertiary carbon positions and the procedure was also less effective for benzylic amines (entry 9). On the other hand, this observation offers the chance for in situ Nef reactions for a one-pot conversion of amines to carbonyl compounds. Initial results in this direction are promising and the elaboration of such a procedure is under investigation.

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Experimental Section

For general methods and instructions see ref.[30]. − Interchangable assignments in the ^{13}C-NMR spectra are marked by *.

Oxidation of Primary Aliphatic Amines to Nitro Compounds. − General Procedure: All reactions were conducted at 22°C under dry nitrogen in a 100-ml dry two-necked vessel equipped with magnetic stirring bar, gas inlet and septum. With exception of **7**, **8a/8b** and **12a/12b** all primary amines (see Table 1) were commercially available and used without further purification. The amino hydrochlorides (**2, 4** and **10**) were converted to the bases by usual NaOH (**2** and **10**) or Na_2CO_3 (**4**) treatment. The mixture (43:57) of the *cis*- and *trans*-4-*tert*-butylcyclohexylamines (**8a/8b**) was obtained by Schmidt degradation of the commercially available *cis*/*trans*-4-*tert*-butylcyclohexanecarboxylic acid.[31]

A solution of the amine (10.0 mmol) in dry CH_2Cl_2 (20 ml) was treated successively with freshly activated powdered molecular sieves (3 Å, 1.5 g) and Zr(O *t*-Bu)$_4$ (0.4 ml, 1.0 mmol). After stirring for 30 min, a solution of TBHP in CH_2Cl_2 (*c* = 3.66 mol/l, 16.0 ml, 59 mmol) was added within 2−5 min. After complete consumption of the starting material (GC control, 1−8 h, see Table 1) the reaction was quenched by addition of water (10−20 ml). The mixture was filtered and the molecular sieves washed carefully with CH_2Cl_2 (50 ml). The organic phase was stirred overnight in presence of a Na_2SO_3 solution (5%, 50 ml) to reduce the excessive TBHP. The organic phase was separated, dried (Na_2SO_4) and purified by column chromatography on silica gel followed by bulb-to-bulb destillation or crystallization (for yields and boiling points see Table 1).

3-(Nitromethyl)-cis-pinane (**14**): $[\alpha]_D^{20}$ = +19.7 (*c* = 0.98, CH_2Cl_2). − IR (neat): $\tilde{\nu}$ = 2911 cm^{-1}, 2873, 1549 (NO_2), 1472, 1455, 1431, 1379 (NO_2). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.19−4.41 (m, 2 H, C*H*$_2$NO$_2$), 2.49−2.62 (m, 1 H, 2-H), 2.32−2.40 (m, 1 H, 7-H), 2.17−2.27 (m, 1 H, 4-H), 1.93−1.99 (m, 1 H, 5-H), 1.70−1.85 (m, 2 H, 1-H, 3-H), 1.55−1.62 (m, 1 H, 4-H), 1.21 (s, 3 H, 8-H), 1.07 (d, *J* = 7.15 Hz, 3 H, 10-H), 1.03 (s, 3 H, 9-H), 0.72 (d, *J* = 9.96 Hz, 1 H, 7-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 82.93 (t, *C*H$_2$NO$_2$), 47.24 (d, C-1), 40.86 (d, C-5), 39.80 (d, C-3), 38.44 (s, C-6), 35.18 (d, C-2), 33.66 (t, C-7), 31.53 (t, C-4), 27.63 (q, C-9), 22.71 (q, C-8), 21.03 (q, C-10). − $C_{11}H_{19}NO_2$ (197.2): calcd. C 66.97, H 9.71, N 7.10; found C 66.93, H 9.65, N 7.09.

1,1-Diethoxy-4-nitrobutane (**15**): IR (neat): $\tilde{\nu}$ = 2977 cm^{-1}, 2932, 2881, 1556 (NO_2), 1444, 1377 (NO_2). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.32−4.46 (m, 3 H, 1-H, 4-H), 3.33−3.65 (m, 4 H, OCH_2), 1.94−2.09 (m, 2 H, 3-H), 1.57−1.68 (m, 2 H, 2-H), 1.12 (t, *J* = 7.05 Hz, 6 H, CH_3). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 102.36 (d, C-1), 75,64 (t, C-4), 61.96 (t, OCH_2), 30.58 (t, C-2), 22.84 (t, C-3), 15,54 (q, CH_3). − $C_8H_{17}NO_4$ (191.22): calcd. C 50.24, H 8.96, N 7.32; found C 50.28, H 8.88, N 7.39.

17β-Nitroestron Methyl Ether (**24b**): M.p. 169−170°C (CH_2Cl_2/*n*-hexane); $[\alpha]_D^{20}$ = +102.4 (*c* = 0.5, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 3069 cm^{-1}, 3018, 2978, 2950, 2935, 2928, 2915, 2879, 2865, 1607, 1541 (NO_2), 1503, 1466, 1448, 1388, 1371 (NO_2). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.24 (d, $J_{1,2}$ = 8.55 Hz, 1 H, 1-H), 6.77 (dd, $J_{1,2}$ = 8.55 Hz, $J_{2,4}$ = 2.70 Hz, 1 H, 2-H), 6.68 (d, $J_{2,4}$ = 2.56 Hz, 1 H, 4-H), 4.50 (t, $J_{16,17}$ = 8.82 Hz, 1 H, 17-H), 3.82 (s, 3 H, OCH_3), 2.79−3.02 (m, 2 H), 2.56−2.73 (m, 1 H), 2.06−2.46 (m, 4 H), 1.79−1.98 (m, 2 H), 1.32−1.74 (m, 6 H), 0.83 (s, 3 H, 18-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 158.04 (s, C-3), 138.08 (s, C-5), 132.27 (s, C-10), 126.74 (d, C-1), 114.27 (d, C-4), 112.01 (d, C-2), 94.87 (d, C-17), 55.65 (q, OCH_3), 52.49 (d, C-14), 46.48 (s, C-13), 43.99 (d, C-9), 39.21 (d, C-8), 37.68 (t, C-6)*, 30.08 (t, C-16)*, 27.75 (t, C-12)*, 26.80 (t, C-7)*, 25.16 (t, C-11)*, 23.84 (t, C-15)*, 12.62 (q, C-18). − $C_{19}H_{25}NO_3$ (315.41): calcd. C 72.35, H 7.99, N 4.44; found C 72.36, H 7.95, N 4.47.

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