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Hydroxylamine as an ammonia equivalent: access to NH-tetrahydroisoquinolonic derivatives from aldoximes by the Castagnoli–Cushman reaction followed by reduction

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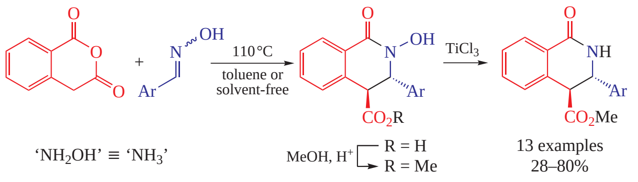
A novel synthetic protocol towards *trans*-NH-tetrahydroisoquinolonic acid esters is based on the Castagnoli–Cushman reaction between aromatic aldehyde oximes and homophthalic anhydride, followed by esterification and $TiCl_3$-promoted reduction. The scope of the method with respect to the aromatic portion (both electron-rich and electron-deficient) is broader compared to the earlier described approaches, which makes it a suitable synthetic strategy for the structure–activity exploration.



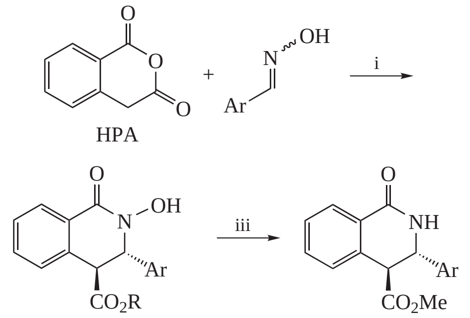
The formal [4+2] cycloaddition of homophthalic anhydride (HPA) and imines (recently dubbed as the Castagnoli–Cushman reaction[1]) offers a facile access to tetrahydroisoquinolonic (THIQ) acids,[2] the promising scaffolds for the design of biologically active compounds.[3] For systematic exploration of the structure–activity relationships around this scaffold, we needed THIQ acids unsubstituted at the lactam nitrogen atom, which would imply using ammonia or its synthetic equivalents.

A limited number of existing reports describe the use of benzylic amines[5,6] or *tert*-butylamine[7] in lieu of ammonia with subsequent removal of the *N*-alkyl substituent. A more straightforward approach relied on application of NH_4OAc as an ammonia component in the Castagnoli–Cushman reaction.[8] However, in our hands this method gave products in suboptimal yield and of insufficient purity. Hence, we considered developing an alternative access to *trans*-NH-THIQ acid derivatives.

Recently, we reported a practically simple approach to *N*-hydroxy THIQ acids **1** *via* the Castagnoli–Cushman reaction of NOH oximes.[9] We reasoned that if a suitable method to deoxygenate these cyclic hydroxamic acids **1** is elaborated, this would constitute a novel general approach to 2-NH-THIQ acids. Herein, we present the results of our investigation in this regard.

Methods for reductive deoxygenation of hydroxamic acids include the use of Zn in acetic acid,[10] hydrobromic acid,[11] molecular hydrogen over Pd catalyst,[12] and $TiCl_3$ in aqueous methanol[13] (though the latter method appears sensitive to the substrate structure[14]). We considered the attractive aspects of using $TiCl_3$ as a reducing agent (its particular propensity to reduce N–O bonds,[15,16] and the opportunity to run the reaction in aqueous methanol[17]) and chose it toward deoxygenation of our *N*-hydroxy THIQ acids **1**.

Initial attempt to reduce representative THIQ acid **1a** with $TiCl_3$ (used as 15% acidic solution in aqueous methanol) resulted in a product mixture difficult for separation. Hence, we decided to convert acid **1a** into its methyl ester **2a** (Scheme 1). To our delight, both the esterification and the subsequent $TiCl_3$ reduction proceeded smoothly and furnished the target NH-THIQ ester **3a** in high yield and purity (with an excellent yield of intermediate ester **2a** obtained in analytically pure form, also without chromatographic purification). These findings were extended to the preparation of NH-THIQ esters **3a–m** *via* a three-step protocol: (1) the Castagnoli–Cushman reaction, (2) esterification and (3) deoxygenation with $TiCl_3$.[†]

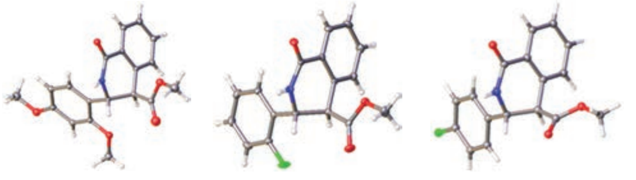


1a–m R = H, 50–88%
2a–m R = Me, 72–97%
3a–m, 28–82%

a Ar = 4-$MeOC_6H_4$
b Ar = 2,4-$(MeO)_2C_6H_3$
c Ar = 3,4-$(MeO)_2C_6H_3$
d Ar = 3-$BnOC_6H_4$
e Ar = 2,6-$(MeO)_2C_6H_3$
f Ar = 4-$Bu^tC_6H_4$
g Ar = 4-$MeSC_6H_4$
h Ar = 3,5-$(MeO)_2C_6H_3$
i Ar = 3-BrC_6H_4
j Ar = 4-$MeOC(O)C_6H_4$
k Ar = 2-FC_6H_4
l Ar = 3,4-$Cl_2C_6H_3$
m Ar = 4-FC_6H_4

Scheme 1 *Reagents and conditions*: i, 110 °C, toluene or solvent-free, 24 h; ii, MeOH, H_2SO_4, room temperature, 18 h; iii, $TiCl_3$, AcONa, MeOH, H_2O, room temperature, 12 h.

[†] *General procedure for the preparation of compounds* **3a–m**. To a vial fitted with a septum and N_2 inlet, hydroxamic acid **2** (0.25–0.63 mmol) and NaOAc (12 equiv.) were added. The vial was flushed with N_2 and methanol–water mixture (1 : 1, 10 ml) was added. Then a 15% solution of $TiCl_3$ (5 ml) was added dropwise within 10 min. The reaction mixture was stirred at room temperature (TLC monitoring, 12 h). The mixture was then diluted with water, extracted with ethyl acetate (3 × 25 ml), the combined organic layers were dried over $MgSO_4$, filtered and concentrated to give essentially pure lactams **3a–c,e,g**. Products **3d,f,h–m** were additionally purified by column chromatography on silica (eluting with 0–0.2% MeOH in CH_2Cl_2).



3b **3k** **3m**

Figure 1 Single-crystal X-ray structures of compounds **3b**, **3k** and **3m**.

In line with the previously reported observations,[9] the Castagnoli–Cushman reaction of electron-rich oximes (synthesis of compounds **1a–h**) proceeded to completion in toluene at 110 °C, while electron-deficient ones (synthesis of compounds **1i–m**) required heating at the same temperature under solvent-free conditions. Esterification toward **2a–m** proceeded generally in excellent yield, and the final deoxygenation provided the target NH-THIQ esters **3a–m** in moderate to excellent yields.

In the reduced products **3**, the initial *trans*-configuration was retained as confirmed by the value of vicinal ^3J coupling constant in the ^{1}H NMR spectrum[9] as well as single-crystal X-ray analysis of the representative compounds **3b**, **3m** and **3k** (Figure 1).[‡]

In summary, we have developed a practically convenient method to prepare NH-THIQ acid esters *via* the recently developed novel version of the Castagnoli–Cushman reaction between homophthalic anhydride and NOH-oximes with subsequent esterification and N–O bond reduction with $TiCl_3$ in aqueous methanol. The products were obtained in good overall yield and required straightforward chromatographic purification or no purification at all. The scope of the reaction compares favorably to the earlier reported approach and makes it a suitable method for the structure–activity relationship exploration around the medicinally important THIQ scaffold.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.05.033.

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Methyl trans*-3-(2,6-dimethoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate* **3e**. Yield 70 mg (82%). White semi-solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.17 (d, 1H, *J* 7.5 Hz,), 7.57–7.45 (m, 1H), 7.41 (m, 1H), 7.31–7.23 (m, 2H), 7.16 (t, 1H, *J* 8.9 Hz), 6.57 (d, 1H, *J* 8.4 Hz), 5.94 (s, 1H), 5.87 (dd, 1H, *J* 9.4, 1.8 Hz), 4.83 (d, 1H, *J* 9.4 Hz), 3.76 (s, 6H), 3.65 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 171.9, 165.4, 159.0, 137.0, 132.2, 130.3, 128.5, 128.1, 127.6, 126.3, 113.5, 104.3, 55.8, 52.1, 48.6, 48.5. HRMS (ESI), *m/z*: 342.1347 $[M+H]^+$ (calc. for $C_{19}H_{20}NO_5$, *m/z*: 342.1336 $[M+H]^+$).

For characteristics of compounds **3a–d**,**f–m**, see Online Supplementary Materials.

[‡] *Crystallographic data*. Crystals of **3b** ($C_{19}H_{19}NO_5$, M = 341.35) are triclinic, space group $P\bar{1}$, at 100 K: a = 9.0077(4), b = 9.6470(5) and c = = 10.7733(5) Å, β = 103.983(4)°, V = 824.56(7) Å^3, Z =2 (Z' = 0.5), d_{calc} = 1.375 g cm^{-3}, λ(MoKα) = 0.71073 cm^{-1}, F(000) = 360.0. Intensities of 15259 reflections were measured with a 'Xcalibur, Eos' diffractometer [λ(MoKα) = 0.71073 Å, ω-scans, $2\theta < 55°$] and 4740 independent reflections (R_{int} = 0.0329) were used in further refinement. The structure was solved by a direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. Hydrogen atoms were located from the Fourier synthesis and refined in the isotropic approximation. The refinement converged to wR_2 = 0.2218 and GOF = = 1.038 for all independent reflections [R_1 = 0.0818 was calculated against F for 3849 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using ShelXS and ShelXL.

Crystals of **3k** ($C_{17}H_{14}FNO_3 \cdot CHCl_3$, M = 418.67) are triclinic, space group $P\bar{1}$, at 100 K: a = 7.9446(2), b = 10.2448(3) and c = 12.3622(3) Å, β = 77.131(3)°, V = 909.18(5) Å^3, Z = 2 (Z' = 0.5), d_{calc} = 1.529 g cm^{-3}, λ(MoKα) = 0.71073 cm^{-1}, F(000) = 360.0. Intensities of 15259 reflections were measured, and 4157 independent reflections (R_{int} = 0.0237) were used in further refinement, which converged to wR_2 = 0.1433 and GOF = = 1.027 for all independent reflections [R_1 = 0.0818 was calculated against F for 3764 observed reflections with $I > 2\sigma(I)$].

Crystals of **3m** ($C_{17}H_{14}FNO_3$, M = 299.29) are monoclinic, space group $P2_1/c$, at 100 K: a = 8.6881(4), b = 13.7850(4) and c = 12.8469(7) Å, β = 108.733(5)°, V = 1457.11(12) Å^3, Z = 4 (Z' = 0.5), d_{calc} = 1.364 g cm^{-3}, λ(MoKα) = 0.71073 cm^{-1}, F(000) = 624.0. Intensities of 12811 reflections were measured, and 3357 independent reflections (R_{int} = 0.0301) were used in further refinement, which converged to wR_2 = 0.1044 and GOF = = 1.036 for all independent reflections [R_1 = 0.0393 was calculated against F for 2788 observed reflections with $I > 2\sigma(I)$].

CCDC 1854031–1854033 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.