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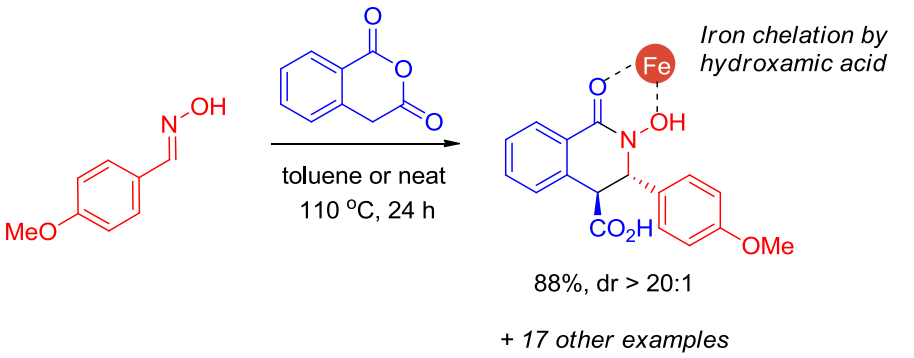
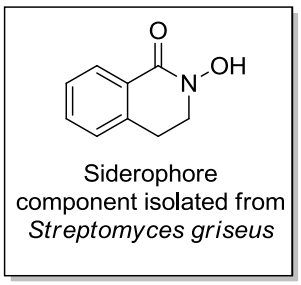


88%, dr > 20:1

+ 17 other examples



Siderophore component isolated from *Streptomyces griseus*

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Iron-Complexing Cyclic Hydroxamic Acid Analogs of Bacterial Siderophores Prepared via the Castagnoli-Cushman Reaction of Unprotected Oximes

Olga Bakulina, Anton Bannykh, Dmitry Dar'in and Mikhail Krasavin*[a]

[a] Dr. O. Bakulina, A. Bannykh, Dr. D. Dar'in, Prof. Mikhail Krasavin

Laboratory of Chemical Pharmacology, Saint Petersburg State University, Saint-Petersburg 199034 Russian Federation

E-mail: m.krasavin@spbu.ru

ORCID: Olga Bakulina: 0000-0002-4930-0739; Anton Bannykh: 0000-0003-1145-0114; Dmitry Dar'in: 0000-0002-0413-7413; Mikhail Krasavin: 0000-0002-0200-4772

Abstract: The first application of multicomponent chemistry (the Castagnoli-Cushman reaction) toward the convenient one-step preparation of cyclic hydroxamic acids is described. The latter are close analogs of bacterial siderophores (iron-binding compounds) and have been confirmed by spectrophotometric measurements to form stable complexes with Fe^{3+} ions. This validates these compounds as potential components for the design of chelating agents for iron overload disease therapy, as well as siderophore-based carrier systems for antibiotic delivery across the bacterial cell wall.

Introduction

Cyclic hydroxamic acid (*N*-hydroxylactam) motifs are widely displayed in natural products as well as synthetic enzyme inhibitors. Their ability to chelate metal ions is the principal determinant of their biological activity. Examples include microbial siderophores (procaryotic matabolites excreted into the extracellular space to scavenge, by chelation, iron needed for growth and differentiation)[1] such as scabichelin (**1**),[2] oxachelin (**2**),[3] and the simple *N*-hydroxy-3,4-dihydroisoquinolin-1-one (**3**) isolated from *Streptomyces griseus*.[4] Chelation to the prosthetic zinc ion is the principal mode of action of HIV integrase inhibitors (such as **4**),[5] matrix metalloprotease inhibitors (exemplified by **5**[6] and **6**[7]) and histone deacetylase inhibitors (such as **7**).[8] However, the *in vivo* effects of cyclic hydroxamic acids extend beyond those mediated by metal chelation: even classical bacterial siderophores have been shown to exert signaling function, antibacterial activity and facilitate adaptation to oxidative stress.[9] Additionally, the *N*-hydroxylactam moiety can function as a nucleophile (rather than metal chelator), which manifests in the mechanism of action of kynurenine aminotransferase II

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inhibitors acting by forming a covalent adduct with pyridoxal phosphate in the enzyme's active site.[10] Finally, iron-loaded bacterial siderophores and their analogs have found utility as co-called 'Trojan horse' carriers for antibiotics and fluorescent labels.[11] Such an approach holds a great promise for circumventing drug resistant bacterial defense mechanism as well as for *in vivo* imaging and eradication of bacterial colonies (teranostics).[12] Removing excess iron from the circulation by chelation is a promising approach to treatment of hereditary iron overload diseases, a therapeutic area very much in need of new non-toxic, orally bioavailable drug candidates.[13] Collectively, the vast applications of cyclic hydroxamic acids in biomedical science justify the development of new, flexible synthetic approaches to this important class of heterocyclic compounds.

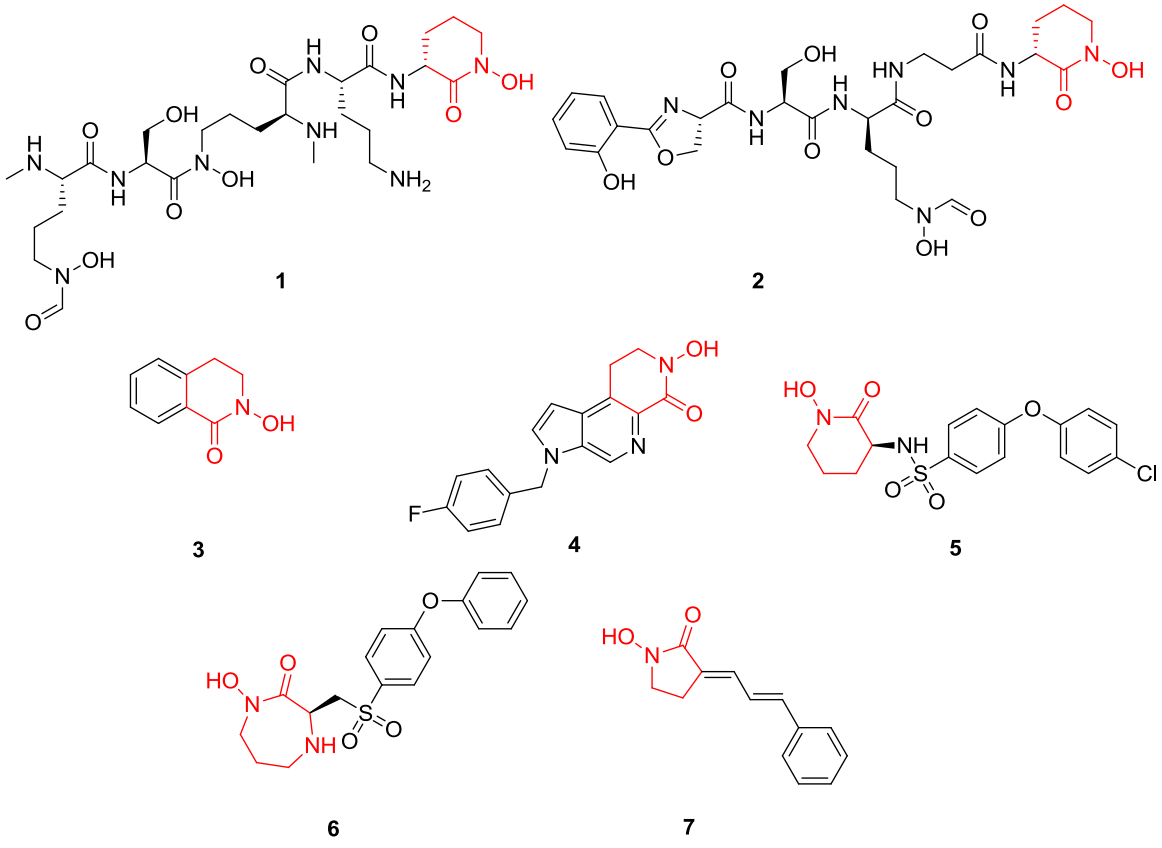

Figure 1. Examples of natural and synthetic biologically active hydroxamic acids acting as metal chelators.

Among the existing synthetic methods for hydroxamic acid, intramolecular nucleophilic cyclization onto *O*-protected acyclic hydroxamic acids,[14] nitroso moiety insertion in cyclic ketones,[15] ring-closing methathesis of bis-olefinic hydroxamic acids[16] are noteworthy. The only multicomponent approach to hydroxamic acids in general involves the use of free[17] or *O*-protected[18] hydroxylamine as an amine component surrogate in the Ugi reaction. However, no

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strategies to access cyclic hydroxamic acids, which would involve multicomponent chemistry, have been described in the literature.

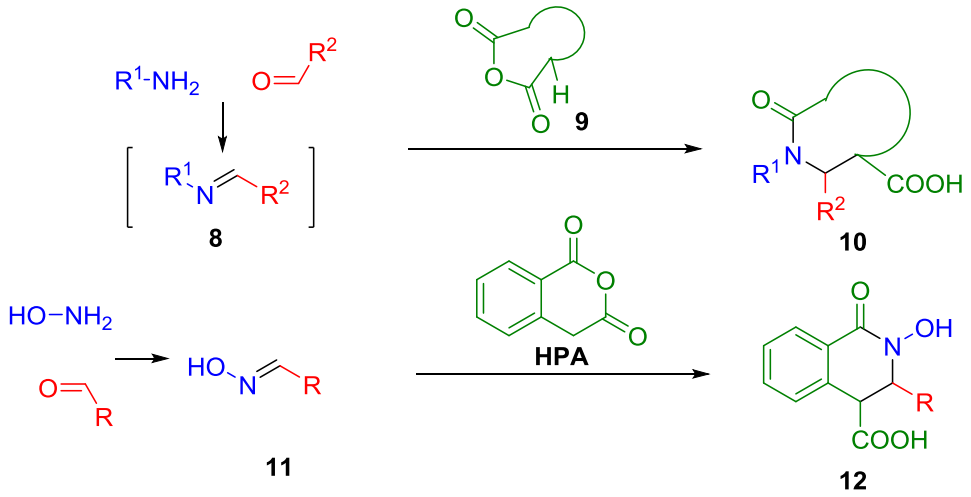


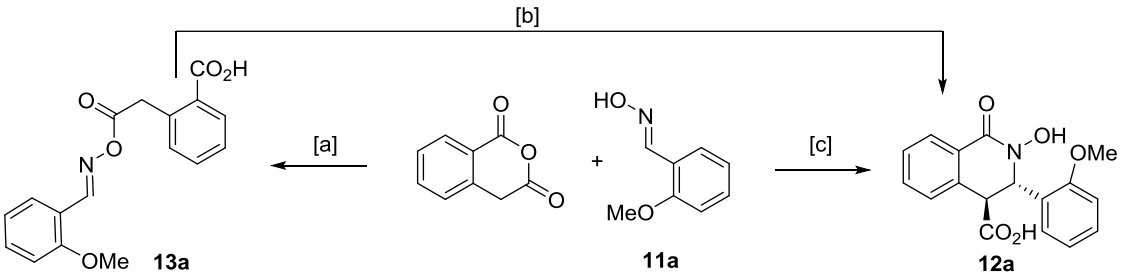
Figure 2. The Castagnoli-Cushman reaction (**8** + **9** → **10**) and its surrogate variant (**11** + **HPA** → **12**) investigated in this work.

Recently, we have been engaged[19] in extending the scope of the Castagnoli-Cushman reaction (CCR),[20] i. e. the reaction of imines **8** (formed *in situ* or in a separate vessel from respective aldehydes and primary amines) with α-C-H dicarboxylic acid anhydrides **9**, which leads to a formal cycloaddition delivering polysubstituted lactams **10** with a full atom economy. We reasoned that employing oximes **11** (either free or *O*-protected) as a surrogate replacement for the imines **8** in this reaction would provide a facile, one-step entry into cyclic hydroxamic acids **12**. Herein, we report on a successful realization of this strategy for homophthalic anhydride (HPA) (Figure 2), which was identified, shortly after the discovery of the CCR, as a particularly suitable partner for the reaction with imines.

Results and Discussion

CCR of homophthalic anhydride with oximes: The nucleophilicity of free oximes toward acylating agents manifested itself in a rapid precipitation of adduct **13a** (which was isolated and fully characterized) from an acetonitrile solution of HPA and oxime **11a**. Overnight heating of this solution to 80 ºC resulted in an appreciable (though incomplete) conversion to desired cyclic hydroxamic acid product **12a**. Conducting the same reaction in refluxing toluene (110 ºC) for 24 hours resulted in full conversion and 83% isolated yield of compound **12a** (Scheme 1).

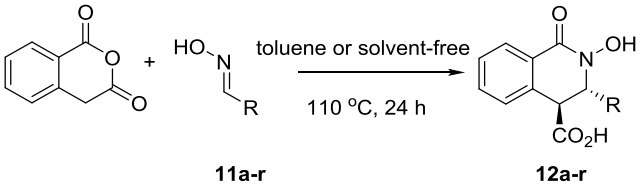
Scheme 1. Identifying conditions for the reaction of oxime **11a** with HPA.

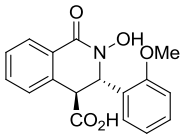
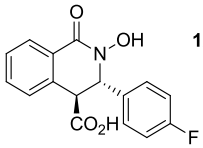
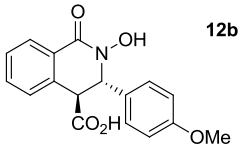
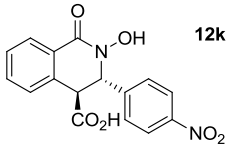
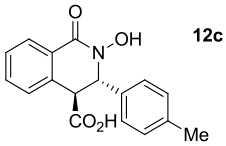
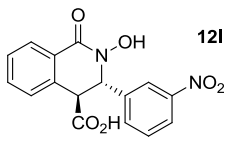


Conditions: [a] MeCN, r. t., 1 h (32%); [b] MeCN, 80 ^{o}C (incomplete conversion, not isolated); [c] toluene, reflux, 24 h (83%, trans/cis>20:1).

This protocol was extended to range of other oximes and the respective products (**12b-i**, entries 1-9) were obtained in moderate to excellent yields predominantly as *trans*-isomer, as judged by the vicinal methine proton coupling constants[21] and confirmed by a single-crystal X-ray structure of compound **12b** (Figure 3). Apparently, the method is primarily applicable to oximes with electron-donating substituents in the aromatic ring (compound **12d**, entry 4 being an exception). However, electron-deficient aromatic oximes (entries 11-18) practically failed to give any desired products under these conditions. This obstacle was circumvented by applying the recently described[19c] solvent-free protocol for the CCR. Products **12j-r** (entries 10-18) containing electron-poor aromatic groups were obtained in high diastereoselectivity, albeit in modest to fair yields (Table 1).

Table 1. Cyclic hydroxamic acids **12a-r** synthesized in this work.



Entry	Structure	Yield[c]	*trans/cis*	Entry	Structure	Yield[c]	*trans/cis*
1[a]	 **12a**	83%	>20:1	10[b]	 **12j**	50%	>20:1
2[a]	 **12b**	88%	>20:1	11[b]	 **12k**	49%	>20:1
3[a]	 **12c**	57%	>20:1	12[b]	 **12l**	64%	>20:1

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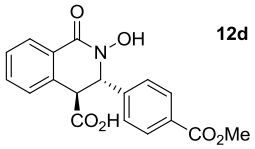
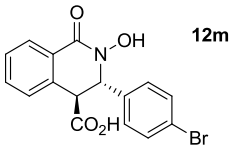
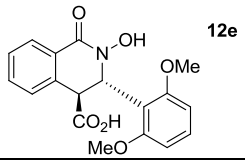
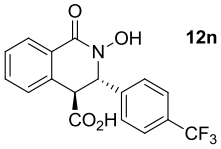
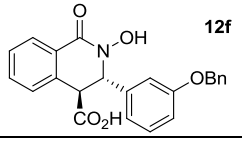
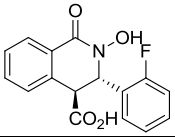
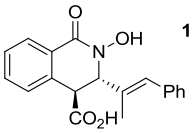
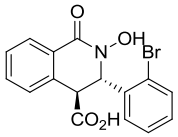
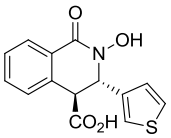
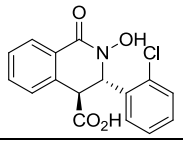
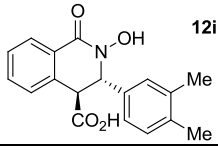
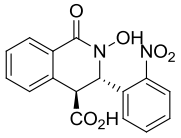
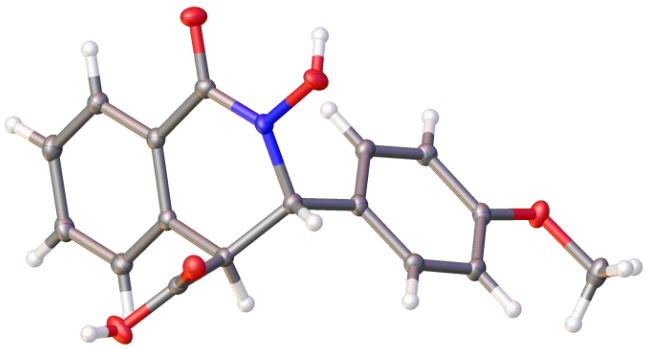
4[a]	 **12d**	74%	11:1	13[b]	 **12m**	44%	>20:1
5[a]	 **12e**	73%	>20:1	14[b]	 **12n**	64%	>20:1
6[a]	 **12f**	76%	12:1	15[b]	 **12o**	60%	>20:1
7[a]	 **12g**	39%	12:1	16[b]	 **12p**	38%	>20:1
8[a]	 **12h**	29%	8:1	17[b]	 **12q**	43%	>20:1
9[a]	 **12i**	43%	7:1	18[b]	 **12r**	36%	>20:1

[a]Reaction conditions: HPA (1 mmol), oxime **11** (1 mmol), toluene (2 mL), 110 °C, 24 h.
[b]Reaction conditions: HPA (1 mmol), oxime **11** (1 mmol), neat, 110 °C, 24 h.
[c]Isolated yield.

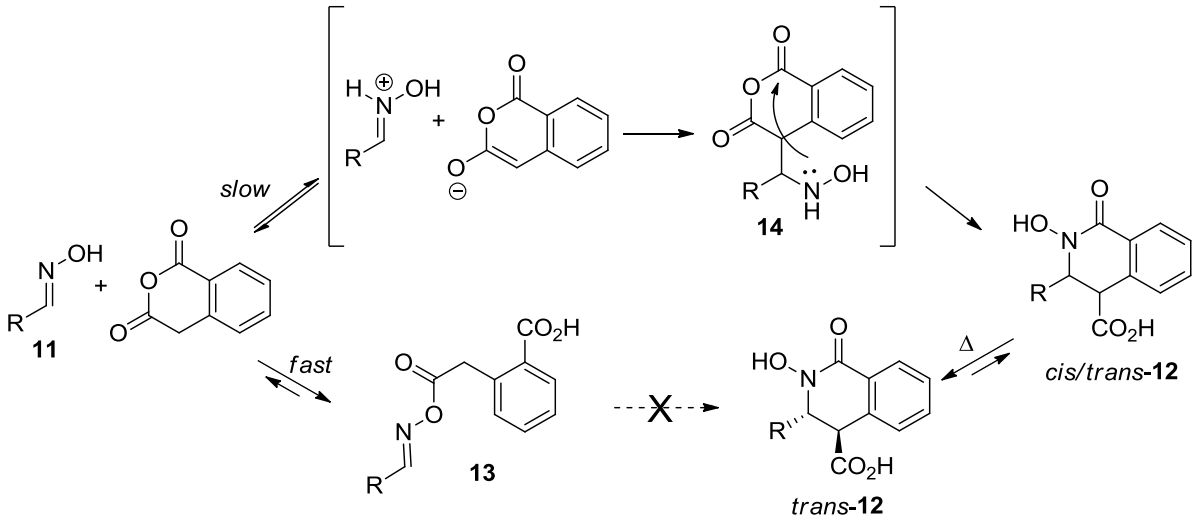
Figure 3. Single-crystal X-ray structure of compound **12b**.



Mechanistic rationale: It is reasonable to expect that oximes **11** (similarly to imines **8**[22]) react with HPA via the initial Mannich type addition of the HPA enolate followed by intramolecular aminolysis of the HPA moiety in intermediate **14** (sterically hindered *N*-alkyl analogs of which have been recently isolated[23] or trapped[24]). The observed behavior of oximes **11** in presence of HPA (*vide supra*) suggests that the formation of Mannich adduct **14** is likely a slow process and the formation of **13** via kinetically favored *O*-acylation dominates. It is difficult to imagine that

13 would transform itself directly to **12**. Being an activated derivative of homophthalic acid, **13** probably exists in equilibrium with HPA, which can eventually give rise to **14** and, ultimately, to final product **12**. The rate of such a transformation (**13**→[**14**]→**12**) most likely depends on the solubility of **13** in the reaction medium and the temperature.

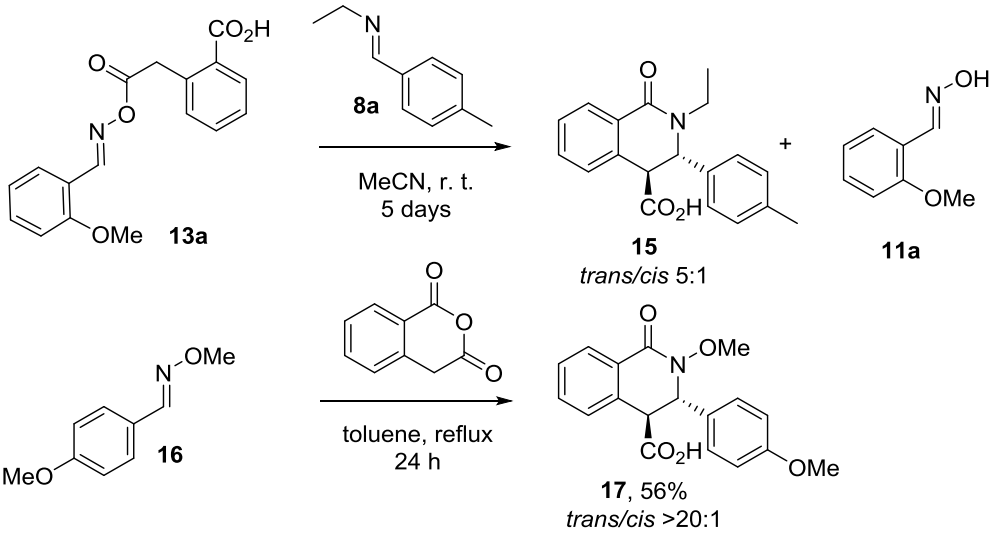
Scheme 2. Mechanistic rationale for the conversion of oximes **11** to cyclic hydroxamic acids **12**.



The following observations (made for oxime **11a**) are consistent with the above mechanistic picture. Exposure of **11a** to HPA in acetonitrile at room temperature resulted in a predominant formation of **13a**. Raising the temperature to 80 ºC (and further to 110 ºC in refluxing toluene) drove the conversion (**13a**→**12a**) forward by increasing the solubility of **13a** and/or accelerating the Mannich addition step. The solubility consideration was substantiated by the full conversion of **13a** to **12a** (obtained as a 1:1 *cis/trans* mixture) observed by ^{1}H NMR of a DMSO-d_6 solution of **13a** at room temperature for 24 h. In the course of this transformation, a gradual appearance of signals from HPA (δ 4.29 ppm) and **11a** (δ 8.32 ppm) was noted followed by emergence of signals corresponding to *cis/trans*-**12a**. Raising the temperature to 110 ºC rapidly equilibrated this mixture to >95% pure *trans*-**12a**.

The idea of *O*-acylation (i. e. the formation of **13**) being in competition with the reaction path leading to **12** - and not required for the formation of the latter – is supported by the following evidence. In one experiment, addition of imine **8a** to a suspension of **13a** in acetonitrile led, after stirring the reaction mixture at room temperature for 5 days, to the formation of tetrahydroisoquinolonic acid **15** (i. e. the CCR product of HPA and **8a**) as a 5:1 *trans/cis* mixture and oxime **11a** (according to ^{1}H NMR analysis of the reaction mixture, see ESI p.S38). In the other experiment, *O*-methyl oxime **16** was exposed to HPA in refluxing toluene, which gave respective CCR product **17** (Scheme 3).

Scheme 3. Experimental results supporting the proposed mechanistic view.



Limitations of the scope: A number of instances when free oximes failed to undergo the CCR with HPA (either in refluxing toluene or neat at elevated temperature) have been noted. Certain sterically hindered (**11s**) or *N*-heteroaromatic (**11t-v**) oximes only gave the corresponding known nitriles **18**, thus HPA was acting solely as a dehydrating agent toward these oximes (Scheme 4).

A number of oximes prepared from a-C-H aldehydes and ketones (**11w-z**, Figure 4) failed to undergo desired transformation on exposure to HPA at 110 ºC (in toluene or neat) yielding complex product mixtures.

Scheme 4. Dehydration of oximes by HPA.

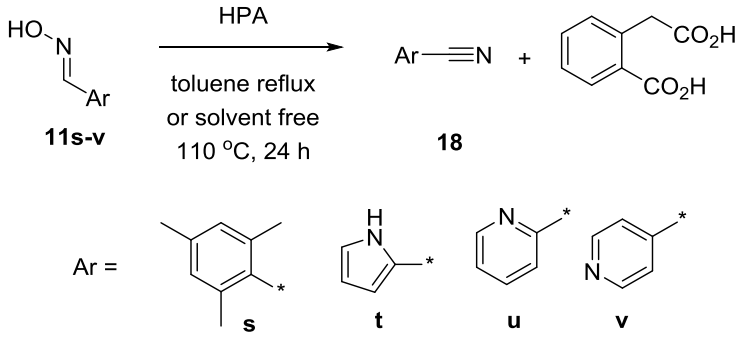
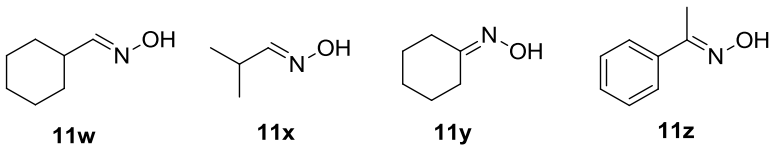
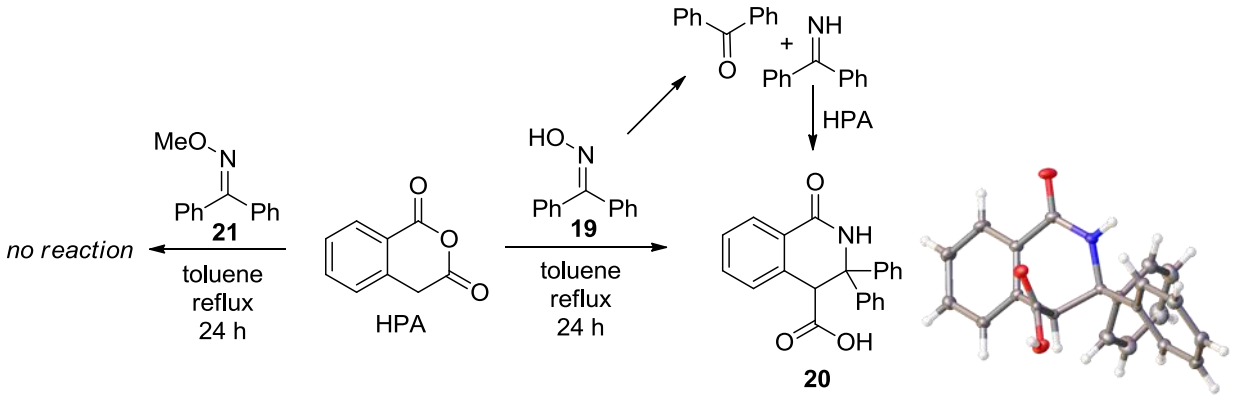


Figure 4. Oximes displaying no reactivity toward HPA.



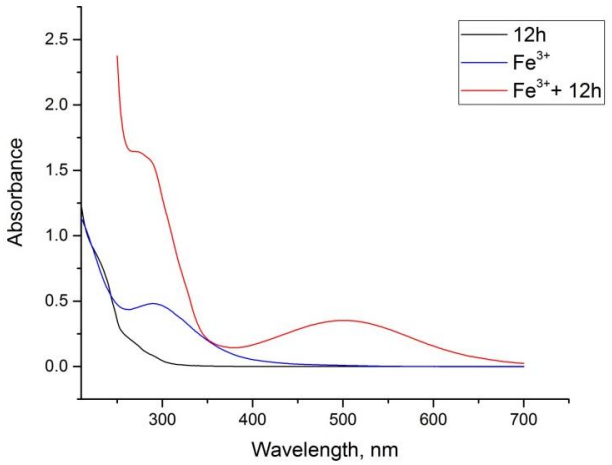
A rather unexpected behavior on reaction with HPA was noted for benzophenone oxime (**19**). After a day of refluxing the two partners in toluene, the sole product of the reaction was the dehydroxylated product **20** which was isolated in 45% yield and fully characterized by $^{1}H/^{13}C$ NMR spectroscopy, high-resolution mass spectrometry and single-crystal X-ray analysis. This result can be rationalized by the known[24] propensity of benzophenone oxime to disproportionate into a mixture of benzophenone and benzophenone imine. The latter can indeed give rise to **20** via a regular CCR.[25] This view is supported by the absence of any conversion in the reaction of *O*-methyl benzophenone oxime (**21**) with HPA (Scheme 5).

Scheme 5. Benzophenone oxime (**19**) in CCR with HPA.



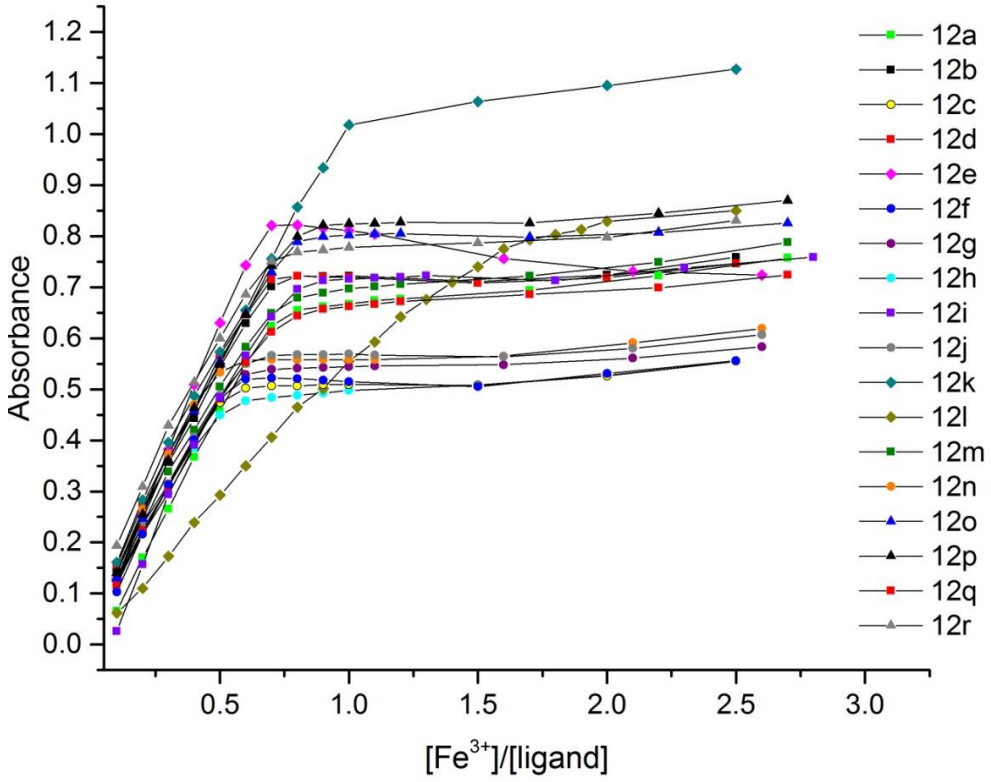
Fe^{3+} binding studies: Compounds **12a-r** synthesized in the course of this study are direct analogs of bacterial siderophores (of **3** in particular) and, therefore, can be potentially regarded as structurally new Fe^{3+}-sequestering components for iron overload disease therapy and for the design of novel iron-loaded 'Trojan horse' carriers for antibiotic transport across bacterial cell wall. Hence, we proceeded to confirm that the new cyclic hydroxamic acids are indeed competent complexing agents for iron. Additionally, we aimed to assess stoichiometry and stability (formation constants or K_f) of respective complexes. Complexation of Fe^{3+} with **12** can be monitored spectophotometrically by the appearance of new a band in the visible region (with maximum around 500 nm) while individual $FeCl_3$ and ligand solutions do not absorb in the same range (Figure 5, ESI). Formation of dark red or purple complexes insoluble in water was observed upon addition of iron chloride to **12a-r** solutions.

Figure 5. Absorbance spectra of $FeCl_3$, compound **12h** and the resultant complex [Fe^{3+}-**12h**] in aqueous ethanol.



Spectrophotometric observation of Fe^{3+} binding by compounds **12a-r** in aqueous ethanol (ESI) confirmed efficient formation of the respective complexes. Applying the mole ratio method allowed us to determine not only their stoichiometry but also the associated K_f values.[26-29] Absorbance at characteristic wavelengths (selected individually for each ligand) was plotted as function of [Fe^{3+}]/[ligand] ratio to give curves shown in Figure 6.

Figure 6. Absorbance *vs.* [Fe^{3+}]/[ligand] mole ratio plot for Fe^{3+}-**12a-r** complexes in aqueous ethanol.



In these plots, the position of the curve's bending point on the X-axis (determined from the intersect point of bilinear fitting of experimental curve) indicates the average stoichiometry of the complex. It is evident that compounds **12c**, **12f-h** and **12n** gave a clear-cut 1:2 metal-to-ligand ratio. Only one compound (**12k**) formed a 1:1 complex with Fe^{3+} while the rest displayed the formation of two complexes of 1:1 and 1:2 stoichiometry (proposed structures of which are shown in Figure 7). In general, K_f values for 1:1 complexes were found to be two orders of magnitude larger compared to 1:2 (Table 2). Surprisingly, compound **12l** showed only weak complexation of iron.

Figure 7. Proposed structures of Fe^{3+}-**12** complexes.

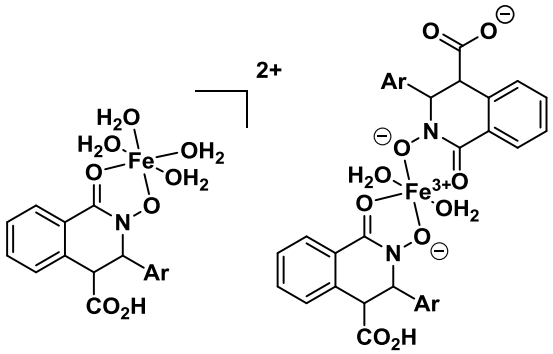


Table 2. Stoichiometry and K_f values for Fe^{3+}-**12** complexes determined by mole ratio method

Ligand, L	Fe:L	K_f	logK_f	λ, nm[a]	Compound	Fe:L	K_f	logK_f	λ, nm[a]
12a	1:1	4.9×10^{8}	8.69	467	**12j**	1:1	1.2×10^{9}	9.08	480
	1:2	1.8×10^{6}	6.26			1:2	1.1×10^{8}	8.04	
12b	1:1	1.1×10^{9}	9.04	465	**12k**	1:1	5.7×10^{7}	7.76	469
	1:2	6.6×10^{7}	7.82						
12c	1:2	6.4×10^{9}	9.81	482	**12l**	1:1	6.7×10^{5}	5.83	470
						1:2	8.9×10^{2}	2.95	
12d	1:1	2.6×10^{9}	9.41	477	**12m**	1:1	1.1×10^{9}	9.04	470
	1:2	8.2×10^{7}	7.91			1:2	8.7×10^{7}	7.94	
12e	1:1	7.2×10^{8}	8.86	470	**12n**	1:2	8.4×10^{9}	9.92	477
	1:2	2.3×10^{7}	7.36						
12f	1:2	3.6×10^{9}	9.56	465	**12o**	1:1	4.5×10^{8}	8.65	474
						1:2	9.8×10^{5}	5.99	
12g	1:2	2.5×10^{9}	9.39	482	**12p**	1:1	2.1×10^{8}	8.32	472
						1:2	1.2×10^{6}	6.08	

12h	1:2	5.1×10^{9}	9.71	481	**12q**	1:1	1.0×10^{9}	9.00	467
						1:2	3.0×10^{6}	6.48	
12i	1:1	3.7×10^{8}	8.57	465	**12r**	1:1	2.0×10^{8}	8.30	462
	1:2	2.1×10^{7}	7.32			1:2	2.8×10^{6}	6.45	

[a] Characteristic absorbance wavelength at which absorbance of the complex was measured.

Conclusions

We have described a simple and facile entry into cyclic hydroxamic acids, an important class of compounds endowed with diverse biological activities, most of which are mediated by the ability of this compounds to chelate metals. The approach is the first application of multicomponent chemistry in general (and of the Castagnoli-Cushman reaction in particular) toward the construction of cyclic hydroxamic acids. The latter have been shown to form strong complexes with Fe^{3+} ions. This process can be monitored spectrophotometrically and the mole ratio method offers a convenient way to determine the stoichiometry of the complexes as well as associated values of the formation constants (K_f). Extension of these findings to other dicarboxylic acid anhydrides as well as evaluation of the pharmacological potential of this new type of cyclic hydroxamic acids are currently underway in our laboratories and will be reported in due course.

Experimental Section

General information: NMR spectroscopic data were recorded with Bruker Avance 400 spectrometer (400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C) in DMSO-d_6 and in $CDCl_3$ and were referenced to residual solvent proton signals (δ_H = 7.26 and 2.50 ppm, respectively) and solvent carbon signals (δ_C = 77.0 and 39.5 ppm, respectively). Melting points were determined with a Stuart SMP50 instrument in open capillary tubes and are uncorrected. Mass spectra were recorded with a Bruker Maxis HRMS-ESI-qTOF spectrometer (electrospray ionization mode). Single crystal X-ray data were obtained from Xcalibur, Eos (monochromated Mo*Kα* radiation, λ = 0.71073 Å) and SuperNova, Atlas (monochromated Cu *Kα* radiation, λ = 1.54184 Å) diffractometers. Absorbance spectra were recorded on Shimadzu UV-1800 spectrophotometer for 85% aqueous ethanol solutions. Toluene was distilled from sodium and stored over MS 4Å. Oximes were synthesized according to known procedures[30] as E/Z isomeric mixtures. Homophthalic anhydride (HPA) and $FeCl_3\cdot6H_2O$ were obtained from commercial sources.

General procedure 1. Toluene protocol. Synthesis of compounds 12a-i, 17 and 20.

A mixture of homophthalic anhydride and corresponding oxime **11a-i, 16** or **19** (1.0 equiv.) was suspended in dry toluene (2 mL/mmol) in a screw-cap vial and was placed in a pre-heated oil bath at 110 ^{o}C. After 24 h the reaction mixture was cooled to room temperature. Compounds **12a**,**b**,**d**,**e** and **20** precipitated from the reaction mixture and were purified by filtration and washing with small amount of cold diethyl ether. Compounds **12c,f-i and 17** were purified by another procedure: the reaction mixture was concentrated, redissolved in DCM (5 mL/mmol) and extracted with saturated aq. $NaHCO_3$ (10 mL/mmol). The aqueous layer was separated and washed with DCM (5 mL/mmol). The pH of aqueous phase was then adjusted to 1 with concentrated aq. HCl at 0 °C. The formed precipitate was collected, washed with small amount of water and dried in air to afford pure products.

General procedure 2. Neat protocol. Synthesis of compounds 12j-r.

A mixture of homophthalic anhydride and corresponding oxime **11j-r** (1.0 equiv.) was placed in a screw-cap vial and was thoroughly ground with a spatula. The vial was placed in a pre-heated oil bath at 110 ^{o}C. After 24 h the reaction mixture was cooled to room temperature. For compounds **12l-r**: a small amount of diethyl ether (5 mL/mmol) was added and the reaction mixture was sonicated in ultrasonic bath for 15 minutes. The resulting suspension was cooled to –20 °C, filtered and dried in air to give pure title compounds. Compounds **12j,k** were purified by another procedure: the reaction mixture was dissolved in DCM (5 mL/mmol) under sonication and was extracted with saturated aq. $NaHCO_3$ (10 mL/mmol). The aqueous layer was separated and washed with DCM (5 mL/mmol). The pH of aqueous phase was then adjusted to 1 with concentrated aq. HCl at 0 °C. The formed precipitate was collected, washed with small amount of water and dried in air to afford pure title compounds **12**.

***trans*-2-Hydroxy-3-(4-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (12b)** was prepared according to general procedure 1 from HPA (162 mg, 1 mmol) and 4-methoxybenzaldehyde oxime **11b** (151 mg, 1 mmol). Yield 275 mg, 88%. White solid, m.p. 224−226 °C. ^{1}H NMR (400 MHz, DMSO-*d*6) δ 13.05 (s, 1H), 10.18 (s, 1H), 7.94 (d, *J* = 7.4 Hz, 1H), 7.56 – 7.35 (m, 2H), 7.29 (d, *J* = 7.1 Hz, 1H), 7.04 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 5.42 (s, 1H), 4.23 (s, 1H), 3.68 (s, 3H). ^{13}C NMR (101 MHz, DMSO-*d*6) δ 172.4, 160.7, 159.1, 133.5, 132.2, 131.0, 130.2, 129.1, 128.3, 127.7, 127.0, 114.3, 65.1, 55.5, 52.0. UV/Vis (EtOH-H_2O): λ^{max} (logε) = 255 nm (3.89). HRMS (ESI), m/z calcd for $C_{17}H_{16}NO_5$ $[M+H]^+$ 314.1023, found 314.1012.

***trans*-3-(4-Trifluoromethylphenyl)-2-hydroxy-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (12n)** was prepared according to general procedure 2 from HPA (162 mg, 1 mmol) and 4-trifluoromethylbenzaldehyde oxime **11n** (189 mg, 1 mmol). Yield 225 mg, 64%. White solid, m.p. 220−222 °C.^{1}H NMR (400 MHz, DMSO-d_6) δ 13.16 (s, 1H), 10.37 (s, 1H), 7.96 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.50 – 7.40 (m, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.29 (dd, *J* = 7.1, 1.6 Hz, 1H), 5.60 (d, *J* = 1.8 Hz, 1H), 4.36 (d, *J* = 1.8 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-*d*6) δ 172.0, 160.9, 143.9 (q, J_{CF} = 1.1 Hz), 133.1, 132.4, 130.2, 128.8, 128.7 (q, *J* = 31.6 Hz), 128.5, 127.5, 127.1, 125.9 (q, J_{CF} = 3.5 Hz), 127.2 (q, J_{CF} = 270.0 Hz), 65.3, 51.5. UV/Vis (EtOH-H_2O): λ^{max} (logε) = 255 nm (3.60). HRMS (ESI), m/z calcd for $C_{17}H_{13}F_3NO_4$ $[M+H]^+$ 352.0791, found 352.0806.

Supporting Information

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.2017xxxxx.

All experimental details can be found in the Supporting Information. This material includes compound characterization data, copies of NMR spectra of the new compounds, X-ray crystallographic information, details of the spectrophotometric Fe^{3+} binding measurements. CCDC 1563858 (**12b**), 1563859 (**17**) and 1563860 (**20**) 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.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: multicomponent chemistry, Castagnoli-Cushman reaction, homophthalic anhydride, cyclic hydroxamic acids, iron chelation, siderophores, spectrophotometry, absorbance, molar ratio, complex stability, stoichiometry.

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