Synthesis of α-Imino Oximes from α-Hydroxyimino Ketones

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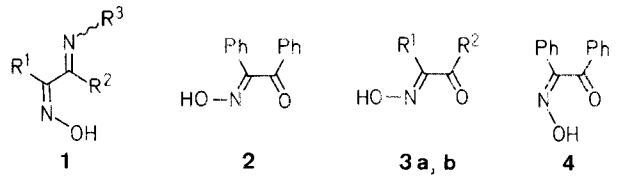
The facile synthesis of a series of novel α-imino oximes from 1,2-dicarbonyl compounds is described. The route involves titanium(IV) chloride catalyzed condensation of amines to the stable and readily available monooximes of 1,2-dicarbonyl compounds.

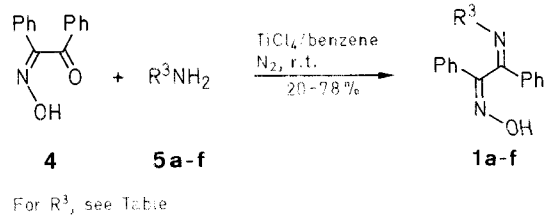
Interest has been shown over the years in molecules, which are capable of forming coordination complexes with metal ions. Among such compounds are substituted diazadienes,[1] oxo oximes,[2] and imino oximes.[3] Our interest in this last type of molecule stems from our research into the synthesis and reactivity, both photochemical and thermal, of unsaturated imine systems.[4] Previously we have noted[5] that it is difficult to achieve condensation of an amine with a monoimine of a poorly reactive 1,2- or 1,3-diketone under the more usual reaction conditions. This difficulty is also present in the reaction of amines with monooximes of 1,2-dicarbonyl compounds. We have observed that this lack of reactivity can be overcome by the use of titanium(IV) chloride, previously used by others[6] for the synthesis of imines, and we report the use of this method in the synthesis of a series of novel α-imino oximes.

A general method for the synthesis of α-imino oximes **1** has not been described. The only examples in the literature for the synthesis of this class of compounds refer to the reactions of the *E*-isomers of both benzil- **2** and biacetyl- **3a** monooximes with aniline.[7,8] However, in the case of benzil, both the *E*- **2** and the *Z*-isomers **4** can be obtained from reaction of benzil with hydroxylamine. In this case, the *Z*-isomer is the more stable and by far the more abundant product. This *Z*-isomer is unreactive under conditions where the α-imino oximes can be prepared from the *E*-isomers and amines.[2] The failure of *Z*-isomers to react is a serious drawback in the synthesis of α-imino oximes. The non-reactivity of the *Z*-isomers can be overcome by the use of titanium(IV) chloride as catalyst. By means of this catalyst it has been possible to carry out the condensation of both *E*- and *Z*-isomers of α-oxo oximes with a series of amines **5** at room temperature and under mild conditions.



1 **2** **3a, b** **4**

α-Oxo oxime **4** was prepared by the method previously described.[9] The α-oxo oximes **3a, b** are commercially available and are in the *E*-form.[10] The α-oxo oxime **4** was reacted with a variety of amines **5** in dry benzene under nitrogen at room temperature for three days with an excess of titanium(IV) chloride (Scheme **A**). α-Oxo oximes **3** were also reacted with isopropylamine (**5b**) (Scheme **B**). Work-up of all of these reaction mixtures in a conventional manner afforded variable yields (20–92%) of the desired α-imino oximes **1a–h**. The majority of the α-imino oximes **1** are obtained in high yield and only **1c** and **1e** are formed in yields < 50%. The failure to obtain high yields in these examples could be due to the formation of organometallic complexes of titanium, which are more stable than those in the other examples. This enhanced stability of complexes from the α-imino oximes **1c** and **1e** could be due to the less hindered sites around the imine nitrogen, a feature, which has been recognized in other systems.[3] The greater stability of the complexes from α-imino oximes **1c** and **1e** could explain loss during work-up.

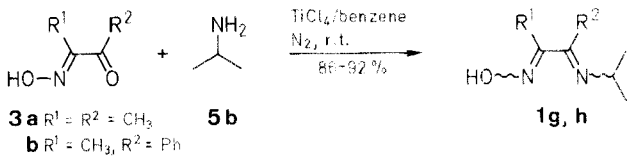


4 **5a-f** **1a-f**

For R^3, see Table

Scheme **A**

All of the α-imino oximes are stable with the exception of **1g** and no special precautions are required for their storage. The gross structure of the α-imino oximes **1** and the presence of one isomer only is obvious from the spectroscopic data shown in the Table. Compound **1f** is the only one to show the existence of another isomer in the ^{13}C-NMR spectrum. It is likely that the imino oximes **1a–f** exist with the imine in the *Z*-configuration in agreement with previous studies.[11] The assignment of stereochemistry to the oximino group relies on the shift of the ^{1}H-NMR position of the oxime hydrogen in dimethyl sulfoxide-d_6.[12] The ^{1}H-NMR spectra show the oxime proton at δ = ca. 11.5. However, irradiation[13] of **1b** brings about *Z*/*E*-isomerization of the hydroxyimino group moving the resonance position of the OH by 0.4 ppm downfield from that of **1b**. This permits the assignment of a *Z*-configuration to **1b** in agreement with previous results.[12] On this basis the imino oximes **1a–e** have the *Z*,*Z*-configuration.



3a $R^1 = R^2 = CH_3$
b $R^1 = CH_3$, R^2 = Ph

5b **1g, h**

Scheme **B**

The α-imino oximes **1g** and **1h** are soluble in chloroform-*d* and these compounds show the oxime hydrogen in the ^{1}H-NMR spectra in the 7.6–9.6 ppm range. The use of dimethyl sulfoxide-d_6 with compound **1h** again shifts this resonance to around δ = 11.5 but with **1g** the oxime hydrogen still resonates at δ = 9.0. The failure of the oxime proton in **1g** to exhibit solvent effects in changing from chloroform-*d* to dimethyl sulfoxide-d_6 could be explained assuming that **1g** is present in the *E*-imine, *Z*-oxime configuration. This change in configuration is brought about by the reduced bulk around the imine moiety.

Melting points were determined on a Büchi 510D apparatus in open capillaries and are uncorrected. IR spectra were recorded on a Perkin-Elmer 257 spectrophotometer and band positions are reported in wavenumbers. ^{1}H- and ^{13}C-NMR spectra were recorded on Varian T60A and Varian FT80A spectrometers, respectively with chemical shifts expressed in ppm downfield from TMS. Elemental analyses were performed by the Consejo Superior de Investigaciones Cientificas, Madrid.

Synthesis of α-Imino Oximes; General Procedure:
A solution of the monooxime **3** or **4** (9 mmol) and the amine **5a–f** or **5b**, respectively, (266 mmol) in benzene (200 mL) is placed in a 500 mL

Table. α-Imino Oximes **1a–h** Prepared

Product	R^1	R^2	R^3	Yield (%)	mp (°C)	Molecular Formula[a] or Lit. mp (°C)	IR (KBr) ν (cm^{-1})	^{1}H-NMR[b] δ, J (Hz)	^{13}C-NMR,[b] (δ) C=N	^{13}C-NMR,[b] (δ) C=N–OH
1a	Ph	Ph	Ph	78	210–211	211[2]	3300–2500 (OH); 1610 (C=N)	6.9–7.3 (m, 13H, Ph); 7.4–7.7 (m, 2H, Ph); 11.5 (s, 1H, OH)	162.8	152.5
1b	Ph	Ph	*i*-Pr	68	185–186	$C_{17}H_{18}N_2O$ (266.3)	3300–2400 (OH); 1620 (C=N)	0.9–1.3 (dd, 6H, J = 7, $2CH_3$); 3.5 (sept, 1H, J = 7, CH); 7.2–7.7 (m, 10H, Ph); 11.6 (s, 1H, OH)	158.9	152.5
1c	Ph	Ph	$PhCH_2$	20	160–161	$C_{21}H_{18}N_2O$ (314.4)	3300–2500 (OH); 1620 (C=N)	4.6 (s, 2H, CH_2); 7.2–7.8 (m, 15H, Ph); 11.8 (s, 1H, OH)	162.5	152.0
1d	Ph	Ph	*t*-Bu	73	183–184	$C_{18}H_{20}N_2O$ (280.4)	3300–2400 (OH); 1610 (C=N)	1.2 (s, 9H, $3CH_3$); 7.1–7.8 (m, 10H, Ph); 11.5 (s, 1H, OH)	155.3	154.9
1e	Ph	Ph	*n*-Bu	35	158–159	$C_{18}H_{20}N_2O$ (280.4)	3300–2500 (OH); 1620 (C=N)	0.6–1.0 (m, 3H, CH_3); 1.1–2.0 (m, 4H, $2CH_2$); 3.5 (t, 2H, J = 7, CH_2N); 7.2–7.6 (m, 8H, Ph); 7.6–8.0 (m, 2H, Ph); 9.6 (s, 1H, OH)	162.5	154.2
1f	Ph	Ph	$PhCH(CH_3)$	52	142–144	$C_{22}H_{20}N_2O$ (328.4)	3300–2500 (OH); 1615 (C=N)	1.2–1.6 (dd, 3H, J = 7, CH_3); 4.5 (q, 1H, J = 7, CH); 7.2–7.9 (m, 15H, Ph); 11.6 (br s, 1H, OH); 11.8 (br s, 1H, OH)	160.0	152.0, 152.4
1g	CH_3	CH_3	*i*-Pr	86	oil	$C_7H_{14}N_2O$ (142.2)	3500–2700 (OH); 1630 (C=N)	1.1 (d, 6H, J = 6, $2CH_3$); 1.9 (s, 3H, CH_3); 2.0 (s, 3H, CH_3); 3.7 (sept, 1H, J = 6, CH); 9.0 (s, 1H, OH)	161.6	157.7
1h	CH_3	Ph	*i*-Pr	92	124–126	$C_{12}H_{16}N_2O$ (204.3)	3500–2700 (OH); 1610 (C=N)	1.0 (d, 6H, J = 6, $2CH_3$); 2.0 (s, 3H, CH_3); 3.3 (sept, 1H, J = 6, CH); 6.8–7.4 (m, 5H, Ph); 11.3 (s, 1H, OH)	164.1	157.5

[a] Satisfactory microanalyses obtained: C ±0.30, H ±0.30, N ±0.30, except **1g** (unstable oil).

[b] TMS is used as the internal standard and spectra are run in DMSO-d_6 except for compound **1g**, which is run in $CDCl_3$.

three-necked round-bottomed flask, equipped with a magnetic stirring bar, a 100 mL pressure equalizing addition funnel with a septum, a N_2 inlet tube, and a reflux condenser. The system is purged with nitrogen and the reaction flask is cooled to 0–5°C using an ice bath. Benzene (50 mL) is placed in the funnel and $TiCl_4$ (1.47 mL, 13 mmol) is added by syringe. This solution is then added dropwise to the reaction flask over a period of 30 min under N_2. After the addition is complete the mixture is stirred for 3 d at room temperature under a positive pressure of N_2. The mixture is then filtered using a Buchner funnel, the solid residue is washed repeatedly with benzene (6 × 50 mL), and the solvent removed by distillation under reduced pressure. When a non-volatile amine is used, the crude reaction product is dissolved in ether (200 mL) and the excess amine is then removed by repeated extraction with 10% dil. HCl (3 × 100 mL). The ethereal layer is dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The α-imino oximes **1** are purified by crystallization from EtOH except for **1g** that is an oil and decomposes on distillation. Isolated yields after crystallization are recorded (Table).

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(1) Bock, H., Dieck, H. *Chem. Ber.* **1967**, *100*, 228.
(2) Taylor, T.W.J., Ewbank, E.K. *J. Chem. Soc.* **1926**, 2818.
(3) Bose, K.S., Patel, C.C. *J. Indian Chem. Soc.* **1974**, *51*, 315.
(4) Armesto, D., Ortiz, M.J., Perez-Ossorio, R. *J. Chem. Soc. Perkin Trans. 1* **1986**, 2021.
Armesto, D., Ortiz, M.J., Perez-Ossorio, R. *Tetrahedron Lett.* **1981**, 2203.
Armesto, D., Gallego, M.G., Horspool, W.M., Ortiz, M.J., Perez-Ossorio, R. *Synthesis* **1987**, 657.
(5) Armesto, D., Bosch, P., Gallego, M.G., Martin, J.F., Ortiz, M.J., Perez-Ossorio, R., Ramos, A. *Org. Prep. Proced. Int.* **1987**, *19*, 181.
(6) White, W.A., Weingarten, H. *J. Org. Chem.* **1967**, *32*, 213.
Moretti, I., Torre, G. *Synthesis* **1970**, 141.
(7) Garry, M. *Ann. Chim.* **1942**, *17*, 30.
(8) von Auwers, K., Siegfeld, M. *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 788.
(9) von Auwers, K., Meyer, V. *Ber. Dtsch. Chem. Ges.* **1889**, *22*, 537.
(10) Weston, T., Taylor, J. *J. Chem. Soc.* **1931**, 2018.
(11) Garcia Ruano, J.L., Henao, M.A., Molina, D., Perez-Ossorio, R., Plumet, J. *Tetrahedron Lett.* **1979**, 3123.
Garcia Ruano, J.L., Haro, R., Pascual, C., Perez-Ossorio, R., Plumet, J. *An. Quim.* **1979**, *75*, 1657; *C.A.* **1979**, *91*, 38805.
(12) Kleinspehn, G.G., Jung, J.A., Studniarz, S.A. *J. Org. Chem.* **1967**, *32*, 460.
(13) Armesto, D., Gallego, M.G., Horspool, W.M., Ramos, A. *J. Chem. Soc. Perkin Trans. 1* **1989**, in press.