An Easy Transformation of 2-Amino-2-(hydroxyimino)acetates to Carbamoylformamidoximes

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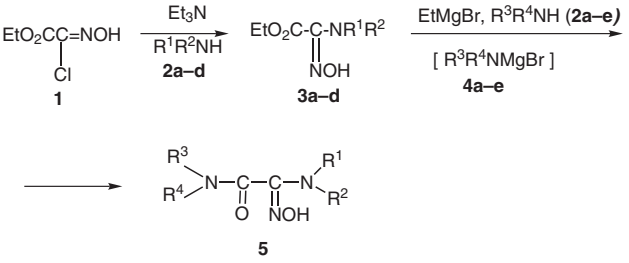
Abstract: Carbamoylformamidoximes **5** are synthesized from 2-amino-2-(hydroxyimino)acetates **3** by reaction with aminomagnesium bromides **4**, prepared in situ from amines **2** and ethylmagnesium bromide.

Key words: amides, amines, amidoximes, amidines, organometallic reagents

Amidoximes possess biological interest due to the presence of a hydroxyimino and an amino function at the same carbon atom. The possibility of varying the substituents at their α-carbon and the two N-containing groups enabled the synthesis of a large number of amidoximes with pronounced biological activity.[1] Meanwhile the substituted carbamoylformamidoximes have a promising synthetic potential, particularly for heterocyclic chemistry. Our continuous interest on amidoximes[1–3] prompted us to synthesize the title compounds, which are the monoximes of the corresponding N^1,N^2-substituted oxalamides. The symmetrically N^1,N^2-substituted bis-oximes of the oxalamides are known, being easily prepared by treatment of dichloroglyoxime or cyanogen di-*N*-oxide with amines.[4,5] Recently[6] unsymmetrical imidoyl derivatives such as 2-(arylamino)-2-(arylimino)acetamides have been reported.

First we attempted unsuccessfully the preparation of the title compounds by treating symmetrical bis-oximes of oxalamides with one equivalent of nitrous acid in analogy to the reported transformation of α-hydroxyiminoamidoximes to α-hydroxyiminoamides.[7] We also tried to synthesize the title compounds **5** via the in situ reaction of the known (phenylcarbamoyl)formonitrile oxide, PhNHCOC≡N→O (prepared by thermal decomposition of α-methoxycarbamoyl-α-nitroacetanilide,[8] or from nitromethane and phenyl isocyanate[9]), with aniline. Both attempts failed, due to the high temperature applied in the first case or the presence of the phenyl isocyanate in the second case. In this paper we wish to report the facile synthesis of the title compounds **5** by the reaction sequence depicted in Scheme 1.



2,3,4: **a**: $R^1 = R^3$ = Ph, $R^2 = R^4$ = H; **b**: $R^1 = R^3$ = 4-MeC_6H_4, $R^2 = R^4$ = H; **c**: $R^1 = R^3$ = c-C_6H_{11}, $R^2 = R^4$ = H; **d**: $R^1 = R^3$ = Ph, $R^2 = R^4$ = Me; **e**: R^3 = Bn, R^4 = H

Scheme 1

Treatment of ethyl 2-chloro-2-(hydroxyimino)acetate (**1**)[10] with triethylamine and amines **2a–d** at room temperature, according to the literature[11] afforded the corresponding 2-amino-2-(hydroxyimino)acetates **3a–d** in 74–97% yield (Table 1). Amidoximes **3a–d** were then treated with aminomagnesium bromides **4a–e**, prepared in situ from the appropriate amines **2a–e** and ethylmagnesium bromide in anhydrous diethyl ether, to give the corresponding title amidoximes **5a–j** in 41–83% yield (Table 2). It is important to be noticed that the C=NOH group remained unchanged during this reaction with the organometallic reagent present under the applied reaction conditions;[12] may be in the first step a metalation takes place leading to a magnesium chelate complex and then the excess of the reagent is capable of substituting the ester function.

To the best of our knowledge no reactions of organometallic compounds and amidoximes have been reported in the literature, while our conditions enable the transformation of an ester group in the α-carbon into an amide. The described method appears to be well suited for both secondary and tertiary amidoximes **3a–d** (R^1 = aryl, alkyl; R^2 = H, Me) and aminomagnesium bromides **4a–e**. The observed low yields in some of the reactions studied are influenced by the stability of the intermediates **4a–e** depending on the reaction conditions. Thus, the yield of the prepared compound **5c** in two efforts was 57 and 83%. No attempt has been made to optimize the yields, which are based on ester compounds **3a–d**. The final isolated products were purified by column chromatography or crystallization.

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Table 1 Preparation of 2-Amino-2-(hydroxyimino)acetates **3**

Entry	Amine **2**	Acetate **3** R^1	R^2	Yield (%)	Mp (°C) (solvent)	Lit. Mp (°C)
1	**2a**	**3a** Ph	H	77	105–106 (EtOH)	105–106[11]
2	**2b**	**3b** 4-MeC_6H_4	H	87	125–127 (CH_2Cl_2–hexane)	–
3	**2c**	**3c** *c*-C_6H_{11}	H	74	69–71 (Et_2O–hexane)	–
4	**2d**	**3d** Ph	Me	75	101–103 (CH_2Cl_2–hexane)	–

Table 2 Preparation of Carbamoylformamidoximes **5**

Entry	Acetate **3**	Amine **2**	Carbamoylformamidoxime **5** R^1	R^2	R^3	R^4	Yield (%)	Mp (°C) (solvent)
1	**3a**	**2a**	**5a** Ph	H	H	Ph	62	187–189 (hexane–EtOAc)
2	**3a**	**2c**	**5b** Ph	H	H	*c*-C_6H_{11}	51	180–182 (hexane–CH_2Cl_2)
3	**3b**	**2a**	**5c** 4-MeC_6H_4	H	H	Ph	83	194–196 (hexane–EtOAc)
4	**3b**	**2b**	**5d** 4-MeC_6H_4	H	H	4-MeC_6H_4	83	189–191 (hexane–EtOAc)
5	**3b**	**2e**	**5e** 4-MeC_6H_4	H	H	Bn	80	168–170 (hexane-CH_2Cl_2)
6	**3c**	**2c**	**5f** *c*-C_6H_{11}	H	H	*c*-C_6H_{11}	64	172–174 (hexane–EtOAc)
7	**3c**	**2a**	**5g** *c*-C_6H_{11}	H	H	Ph	49	72–74 (hexane–CH_2Cl_2)
8	**3c**	**2e**	**5h** *c*-C_6H_{11}	H	H	Bn	41	235–237 (CH_2Cl_2)
9	**3d**	**2a**	**5i** Ph	Me	H	Ph	81	140–142 (hexane–EtOAc)
10	**3d**	**2d**	**5j** Ph	Me	Me	Ph	47	177–179 (hexane–EtOAc)

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were obtained with a Perkin-Elmer 1310 spectrophotometer as Nujol mulls. NMR spectra were recorded on a Bruker AM 300 (300 MHz, and 75 MHz for ^1H and ^{13}C, respectively) using $CDCl_3$ as the solvent and TMS as an internal standard. *J* values are reported in Hz. Mass spectra were determined on a VG-250 spectrometer at 70 eV under Electron Impact (EI) conditions, or on a Perkin Elmer API 100 Sciex Simple quadrupole under Electrospray Ionization (ESI) conditions. High-resolution mass spectra (HRMS) were recorded on an Ionspec mass spectrometer under Matrix-Assisted Laser Desorption-Ionization Fourier Transform Mass Spectrometer (MALDI-FTMS) conditions with 2,5-dihydroxybenzoic acid (DHB) as the matrix. Microanalyses were performed on a Perkin-Elmer 2400-II Element analyzer. Silica gel Nr. 60, Merck A.G. was used for column chromatography. Compound 1 was prepared by a known procedure.[10]

Compounds 3a–d; General Procedure

The amine **2** (10 mmol) was added to a stirred solution of chloroxime **1** (1.52 g, 10 mmol) in Et_2O (75 mL). To this mixture was added dropwise a solution of Et_3N (1.13 g, 1.56 mL, 11 mmol) in Et_2O (30 mL) over 5 min. After stirring at r.t. for 1.5 h, the white precipitate of $Et_3N{\cdot}HCl$ formed was filtered. The filtrate was concentrated, the residue was dissolved in CH_2Cl_2 (20 mL) and the solution was washed with H_2O. The organic layer was dried (Na_2SO_4) and concentrated to give the corresponding amidoxime **3** (Table 1).

Ethyl 2-Anilino-2-(hydroxyimino)acetate (3a)[11]

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.22 (t, 3 H, *J* = 7.6 Hz), 4.26 (q, 2 H, *J* = 7.6 Hz), 6.93 (d, 2 H, *J* = 7.6 Hz), 7.03 (br s, 1 H, exchangeable with D_2O), 7.10 (t, 1 H, *J* = 7.6 Hz), 7.29 (t, 2 H, *J* = 7.6 Hz), 9.41 (br s, 1 H, exchangeable with D_2O).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 13.7, 62.35, 121.0, 123.8, 128.8, 139.05, 143.3, 160.7.

MS (EI): *m*/*z* (%) = 208 (86), 191 (30), 163 (20), 145 (45), 118 (98), 104 (70), 93 (100), 77 (76).

MALDI-FTMS: *m*/*z* calcd for $C_{10}H_{13}N_2O_3$ [M + H]: 209.0921; found: 209.0927.

Ethyl 2-(Hydroxyimino)-2-(4-toluidino)acetate (3b)

IR (Nujol): 3350, 3150, 1715, 1625, 1605 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.22 (t, 3 H, *J* = 7.6 Hz), 2.26 (s, 3 H), 4.24 (q, 2 H, *J* = 7.6 Hz), 6.84 (d, 2 H, *J* = 7.6 Hz), 6.93 (br s 1 H, exchangeable with D_2O), 7.08 (d, 2 H, *J* = 7.6 Hz), 8.62 (br s, 1 H, exchangeable with D_2O).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 13.8, 20.8, 62.3, 121.5, 129.4, 133.8, 136.5, 143.8, 160.8.

MS (EI): *m*/*z* (%) = 222 (49), 159 (23), 133 (28), 132 (66), 131 (76), 91 (100).

Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.61. Found: C, 59.72; H, 6.22; N, 12.59.

Ethyl 2-(Cyclohexylamino)-2-(hydroxyimino)acetate (3c)
IR (Nujol): 3408, 3365, 3180, 3110, 1724, 1625 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.08–1.40 (m, 5 H), 1.34 (t, 3 H, *J* = 7.6 Hz), 1.54–1.64 (m, 1 H), 1.66–1.78 (m, 2 H), 1.91–2.02 (m, 2 H), 3.75–3.88 (m, 1 H), 4.29 (q, 2 H, *J* = 7.6 Hz), 4.94 (br d, 1 H, *J* = 8.9 Hz, exchangeable with D_2O), 8.67 (br s, 1 H, exchangeable with D_2O).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 13.9, 24.8, 25.4, 35.0, 52.0, 62.0, 144.8, 161.3.

MS (EI): *m*/*z* (%) = 214 (55), 197 (100), 169 (22), 151 (23), 132 (43), 56 (45), 43 (53).

MALDI-FTMS: *m*/*z* calcd for $C_{10}H_{19}N_2O_3$ $[M + H]^+$: 215.139; found: 215.1390.

Ethyl 2-(Hydroxyimino)-2-(methylanilino)acetate (3d)
IR (Nujol): 3250, 1710, 1625, 1585 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.15 (t, 3 H, *J* = 7.3 Hz), 3.32 (s, 3 H), 4.18 (q, 2 H, *J* = 7.3 Hz), 6.83 (d, 2 H, *J* = 7.3 Hz), 6.97 (t, 1 H, *J* = 7.3 Hz), 7.27 (t, 2 H, *J* = 7.3 Hz), 9.20 (br s, 1 H, exchangeable with D_2O).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 13.8, 36.3, 62.1, 116.5, 121.7, 129.1, 148.4, 155.5, 168.7.

MS (EI): *m*/*z* (%) = 222 (47), 206 (48), 205 (53), 178 (67), 160 (46), 150 (23), 133 (64), 132 (63), 118 (80), 107 (100).

Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.61. Found: C, 59.57; H, 6.25; N, 12.55.

Compounds 5a–j; General Procedure
Ethyl bromide (3.93 g, 2.69 mL, 36 mmol) was added to a stirred suspension of Mg turnings (0.864 g, 36 mmol) in anhyd Et_2O (30 mL) at r.t. under argon. When the reaction was complete (all Mg had dissolved), a solution of amine **2a–e** (36 mmol) in anhyd Et_2O (8 mL) was added followed at once by a solution of the ester **3a–d** (4.5 mmol) in anhyd Et_2O (25 mL) under the same conditions. The reaction mixture was then refluxed for 0.5 h and stirred at r.t. for a further 2 h. Then it was washed with aq 5% HCl to dissolve the inorganic salts and the excess of amine. The aqueous layer was extracted with EtOAc and the combined organic layers were dried (Na_2SO_4) and concentrated in a rotary evaporator. The residue was purified by column chromatography on silica gel (hexane, EtOAc as eluents) (Table 2).

2-Anilino-2-(hydroxyimino)-*N*-phenylacetamide (5a)
IR (Nujol): 3375, 3300, 3260, 1661, 1622, 1590 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 2.40 (br s, 2 H, exchangeable with D_2O), 7.05 (d, 2 H, *J* = 7.0 Hz), 7.08–7.25 (m, 1 H), 7.30–7.48 (m, 5 H), 7.61 (d, 2 H, *J* = 8.9 Hz), 8.81 (br s, 1 H, exchangeable with D_2O).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 119.8, 122.1, 124.0, 124.8, 128.4, 129.1, 137.0, 142.0, 153.5, 154.1.

MS (EI): *m*/*z* (%) = 255 (100), 238 (19), 132 (20), 119 (66), 104 (57), 93 (74), 77 (68).

MALDI-FTMS: *m*/*z* calcd for $C_{14}H_{14}N_3O_2$ $[M + H]^+$: 256.1086; found: 256.1080.

2-Anilino-*N*-cyclohexyl-2-(hydroxyimino)acetate (5b)
IR (Nujol): 3390, 3260, 3170, 1650, 1628, 1590 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.12–1.50 (m, 5 H), 1.55–1.86 (m, 3 H), 1.90–2.05 (m, 2 H), 3.72–3.88 (m, 1 H), 6.72 (br d, 1 H, exchangeable with D_2O), 6.96 (d, 2 H, *J* = 7.9 Hz), 6.97 (br s, 1 H, exchangeable with D_2O), 7.05 (t, 1 H, *J* = 7.9 Hz), 7.16 (br s, 1 H, exchangeable with D_2O), 7.25 (t, 2 H, *J* = 7.9 Hz).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 24.7, 25.4, 32.7, 48.6, 121.7, 123.5, 128.3, 139.1, 142.8, 159.7.

MS (EI): *m*/*z* (%) = 261 (43), 244 (56), 234 (6), 208 (25), 199 (15), 191 (8), 163 (11), 145 (29), 135 (16), 118 (100).

Anal. Calcd for $C_{14}H_{19}N_3O_2$: C, 64.35; H, 7.33; N, 16.08. Found: C, 64.01; H, 7.19; N, 16.06.

2-(Hydroxyimino)-*N*-phenyl-2-(4-toluidino)acetamide (5c)
IR (Nujol): 3383, 3290, 3275, 1660, 1622, 1590 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 2.30 (s, 3 H), 3.05 (br s, 1 H, exchangeable with D_2O), 6.96 (d, 2 H, *J* = 8.9 Hz), 7.07 (d, 2 H, *J* = 7.6 Hz), 7.13 (t, 1 H, *J* = 7.6 Hz), 7.31 (t, 2 H, *J* = 7.6 Hz), 7.48 (br s, 1 H, exchangeable with D_2O), 7.56 (d, 2 H, *J* = 8.9 Hz), 9.05 (br s, 1 H, exchangeable with D_2O).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 119.8, 122.5, 124.8, 129.0, 129.1, 141.5, 150.0, 150.8, 157.1, 157.8.

MS (EI): *m*/*z* (%) = 269 (28), 252 (12), 251 (18), 223 (4), 222 (6), 133 (100), 132 (71), 131 (37), 119 (48), 118 (52), 107 (36).

Anal. Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 76.06; H, 5.56; N, 15.54.

2-(Hydroxyimino)-*N*-(4-methylphenyl)-2-(4-toluidino)acetamide (5d)
IR (Nujol): 3390, 3350, 3305, 1670, 1625, 1605 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 2.30 (s, 3 H), 2.31 (s, 3 H), 4.08 (br s, 1 H, exchangeable with D_2O), 6.95 (d, 2 H, *J* = 8.9 Hz), 7.07 (d, 2 H, *J* = 7.6 Hz), 7.11 (d, 2 H, *J* = 8.9 Hz), 7.33 (br s, 1 H, exchangeable with D_2O), 7.45 (d, 2 H, *J* = 7.6 Hz), 8.84 (br s, 1 H, exchangeable with D_2O).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 20.8, 20.9, 119.8, 122.3, 128.9, 129.6, 143.2, 143.4, 150.1, 151.9, 157.1, 157.9.

MS (EI): *m*/*z* (%) = 283 (100), 267 (21), 146 (13), 133 (77), 118 (50), 107 (58), 91 (47), 77 (32).

MALDI-FTMS: *m*/*z* calcd for $C_{16}H_{18}N_3O_2$ $[M + H]^+$: 284.1393. Found: 284.1400.

***N*-Benzyl-2-(hydroxyimino)-2-(4-toluidino)acetamide (5e)**
IR (Nujol): 3390, 3270, 3170, 1655, 1635, 1605 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.77 (br s, 1 H, exchangeable with D_2O), 2.31 (s, 3 H), 4.51 (d, 2 H, *J* = 5.9 Hz), 6.88 (d, 2 H, *J* = 8.9 Hz), 7.06 (d, 2 H, *J* = 8.9 Hz), 7.08 (br s, 2 H, exchangeable with D_2O), 7.25–7.35 (m, 5 H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 20.8, 43.7, 122.2, 127.7, 127.8, 128.8, 129.0, 136.5, 142.8, 144.3, 156.0, 160.7.

MS (EI): *m*/*z* (%) = 283 (77), 267 (30), 266 (89), 222 (21), 196 (6), 159 (11), 146 (15), 133 (85), 132 (89), 118 (94), 106 (100).

Anal. Calcd for $C_{16}H_{17}N_3O_2$: C, 67.83; H, 6.05; N, 14.83. Found: C, 67.63; H, 6.16; N, 14.91.

***N*-Cyclohexyl-2-(cyclohexylamino)-2-(hydroxyimino)acetamide (5f)**
IR (Nujol): 3360, 3320, 3250, 1655, 1615 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.11–1.50 (m, 10 H), 1.59–1.85 (m, 6 H), 1.90–2.09 (m, 4 H), 3.72–3.86 (m, 1 H), 3.95–4.12 (m, 1 H), 5.20 (br d, 1 H, *J* = 8.85 Hz, exchangeable with D_2O), 6.11 (br s, 1 H, exchangeable with D_2O), 6.72 (br d, 1 H, *J* = 8.0 Hz, exchangeable with D_2O).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 24.7, 24.8, 25.4, 25.5, 48.4, 52.0, 145.4, 160.1.

MS (EI): *m*/*z* (%) = 267 (35), 251 (100), 235 (8), 219 (21), 186 (9), 168 (72), 151 (35), 140 (43), 131 (19), 123 (53), 108 (91).

Anal. Calcd for $C_{14}H_{25}N_3O_2$: C, 62.89; H, 9.42; N, 15.72. Found: C, 63.15; H, 9.69; N, 15.65.

2-(Cyclohexylamino)-2-(hydroxyimino)-*N*-phenylacetamide (5g)

IR (Nujol): 3400, 3320, 3280, 1662, 1620, 1580 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.08–1.23 (m, 3 H), 1.24–1.39 (m, 2 H), 1.59 (d, 1 H, *J* = 12.8 Hz), 1.70 (d, 2 H, *J* = 12.8 Hz), 2.00 (d, 2 H, *J* = 8.9 Hz), 4.02–4.13 (m, 1 H), 5.28 (d, 1 H, *J* = 8.9 Hz, exchangeable with D_2O), 7.03 (br s, 1 H, exchangeable with D_2O), 7.12 (t, 1 H, *J* = 7.9 Hz), 7.32 (t, 2 H, *J* = 7.9 Hz), 7.54 (d, 2 H, *J* = 7.9 Hz), 8.73 (s, 1 H, exchangeable with D_2O).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 24.8, 25.5, 35.0, 52.1, 119.8, 124.6, 129.1, 137.1, 144.9, 158.9.

MS (EI): *m*/*z* (%) = 261 (18), 244 (53), 162 (24), 147 (10), 132 (14), 120 (32), 108 (100).

Anal. Calcd for $C_{14}H_{19}N_3O_2$: C, 64.35; H, 7.33; N, 16.08. Found: C, 64.75; H, 7.30; N, 15.72.

***N*-Benzyl-2-(cyclohexylamino)-2-(hydroxyimino)acetamide (5h)**

IR (Nujol): 3420, 3330, 3180, 1660, 1635, 1605 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.23–1.80 (m, 8 H), 2.02–2.07 (m, 2 H), 4.08–4.22 (m, 1 H), 4.55 (d, 2 H, *J* = 5.9 Hz), 7.27–7.38 (m, 3 H), 7.42 (d, 2 H, *J* = 6.9 Hz), 7.78 (br d, 1 H, *J* = 8.7 Hz, exchangeable with D_2O), 9.89 (br s, 1 H, exchangeable with D_2O), 10.27 (br t, 1 H, *J* = 5.9 Hz, exchangeable with D_2O).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 23.8, 24.8, 31.5, 44.8, 52.3, 127.8, 128.5, 128.7, 136.4, 151.5, 154.9.

MS (EI): *m*/*z* (%) = 275 (4), 258 (52), 211 (12), 196 (19), 176 (20), 123 (9), 108 (100).

Anal. Calcd for $C_{15}H_{21}N_3O_2$: C, 65.43; H, 7.69; N, 15.26. Found: C, 65.42; H, 7.69; N, 15.27.

2(Hydroxyimino)-2-(methylanilino)-*N*-phenylacetamide (5i)

IR (Nujol): 3300, 3240, 1655, 1630, 1580 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 3.32 (s, 3 H), 6.86 (d, 2 H, *J* = 8.9 Hz), 6.97 (t, 1 H, *J* = 7.9 Hz), 7.12 (t, 1 H, *J* = 6.9 Hz), 7.24–7.40 (m, 4 H), 7.55 (d, 2 H, *J* = 7.9 Hz), 7.94 (br s, 1 H, exchangeable with D_2O), 8.54 (br s, 1 H, exchangeable with D_2O).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 37.1, 116.5, 119.7, 121.7, 124.7, 129.0, 129.1, 137.2, 145.2, 148.4, 158.3.

MS (EI): *m*/*z* (%) = 269 (44), 253 (39), 252 (42), 181 (8), 160 (49), 147 (9), 133 (51), 118 (81).

Anal. Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.72; H, 5.57; N, 15.65.

2-(Hydroxyimino)-*N*-methyl-2-(methylanilino)-*N*-phenylacetamide (5j)

IR (Nujol): 3240, 1650, 1610, 1580 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 2.39 (s, 3 H), 3.08 (s, 3 H), 6.63 (d, 2 H, *J* = 7.9 Hz), 6.89 (d, 2 H, *J* = 6.9 Hz), 6.97 (t, 1 H, *J* = 6.9 Hz), 7.21–7.32 (m, 3 H), 7.39 (t, 2 H, *J* = 7.9 Hz), 8.35 (br s, 1 H, exchangeable with D_2O).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 35.0, 37.9, 117.4, 121.7, 125.8, 127.5, 128.6, 129.3, 142.5, 143.7, 147.9, 159.5.

MS (EI): *m*/*z* (%) = 283 (86), 266 (85), 190 (9), 159 (40), 146 (100), 134 (91), 132 (91), 118 (48).

Anal. Calcd for $C_{16}H_{17}N_3O_2$: C, 67.83; H, 6.05; N, 14.83. Found: C, 67.62; 5.96; N, 14.73.

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References

(1) Nicolaides, D. N.; Varella, E. A. *The Chemistry of Amidoximes,* In *The Chemistry of Acid Derivatives*, Vol. 2; Patai, S., Ed.; Wiley: New York, **1992**, 876–966.
(2) Nicolaides, D. N.; Fylaktakidou, K. C.; Litinas, K. E.; Hadjipavlou-Litina, D. *Eur. J. Med. Chem.* **1998**, 715.
(3) Nicolaides, D. N.; Litinas, K. E.; Vrasidas, I.; Fylaktakidou, K. C. *J. Heterocycl. Chem.* **2004**, *41*, 499.
(4) Coburn, M. D. *J. Heterocycl. Chem.* **1968**, *5*, 83.
(5) Grundmann, C. *Angew. Chem.* **1963**, *75*, 450.
(6) Langer, P.; Schroeder, R. *Eur. J. Org. Chem.* **2004**, 1025.
(7) Khalilova, S.; Poplavskaya, I. *Izv. Akad. Nauk. Kar. SSR, Ser. Khim.* **1988**, 74; *Chem. Abstr.* **1988**, *109*, 169982b.
(8) Shimizu, T.; Hayashi, Y.; Ito, T.; Teramura, K. *Synthesis* **1986**, 488.
(9) Huisgen, R.; Christl, M. *Chem. Ber.* **1973**, *106*, 3291.
(10) Skinner, G. S. *J. Am. Chem. Soc.* **1924**, *46*, 731.
(11) Gilchrist, T. L.; Harris, C. J.; King, F. D.; Peek, M. E.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2161.
(12) Itsuno, S.; Miyazaki, K.; Ito, K. *Tetrahedron Lett.* **1986**, *27*, 3033.