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SYNTHESIS OF 1*H*-INDAZOLES BY REDUCTIVE CYCLIZATION OF *o*-NITRO-KETOXIMES

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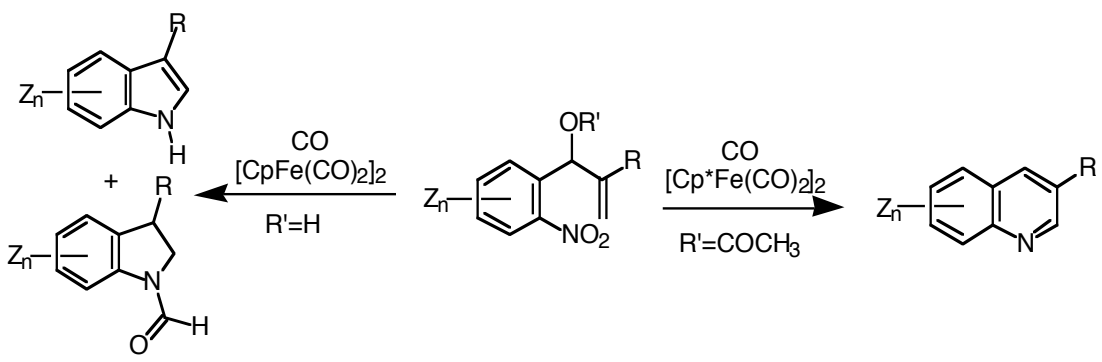
Abstract – *ortho*-Nitro-ketoximes are converted to 1*H*-indazoles upon reaction with carbon monoxide with $[Cp^*Fe(CO)_2]_2$ as catalyst.

INTRODUCTION

Indazoles are important compounds as evidenced by their preponderance in the chemical patent literature as kinase inhibitors[1] and their use as anti-cancer[2] and anti-spermatogenic agents.[3] Indazoles were originally prepared by Fischer,[4] and many syntheses have since been reported.[5] The most widely used methods involve the diazotization of 2-alkylanilines and the cyclization of *ortho*-substituted hydrazones. The former usually requires acidic conditions and works best with electron deficient aromatic substrates while the latter employs hydrazine, a basic reducing agent, and has a similar electronic character. We have been investigating the synthesis of nitrogen heterocycles in our laboratory by the reductive cyclization of *ortho*-substituted nitroaromatics with CO catalyzed by Group 8 metal carbonyl complexes.[6] These reactions, which proceed under neutral, chemoselective conditions, have provided new routes to indoles[6a] and quinolines[6b] (Scheme 1).

Scheme 1

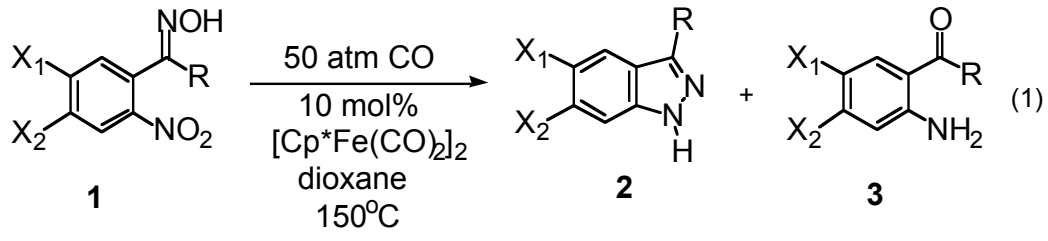


Although the reductions of *o*-nitrobenzylanilines[7] and *o*-nitroimines[8] provide a route to 2-arylindazoles, to our knowledge, the conversion of o-nitroketoximes to 1*H*-indazoles has not been reported. Von Auwers prepared indazoles from benzaldoxime acetates bearing *o*-tosyl-[9] or *o*-acyl-amino groups.[10] Others have shown that sydnones with pendant oxime units cyclize under acidic conditions to give 1*H*-indazoles[11] and that *o*-azidobenzaldoximes give 2-hydroxyindazoles upon boiling in alkali.[12] These conditions are not suitable for substrates bearing acid/base sensitive groups.

The ability of metal carbonyl/CO systems to deoxygenate $RNO_{1,2}$ compounds,[13] as well as N-O bonds in isoxazoles[14] and other heterocycles[15] has been established. We were intrigued by an early report by Alper on the formation of ketones from ketoximes with $Fe(CO)_5/BF_3{\cdot}Et_2O$[16] in which it was suggested that the keto-oxygen originated from the oxime oxygen. Others have since reported similar behavior.[17] We wondered about possible reductive transformations of substrates bearing both oxime and nitro groups, anticipating the discovery of new cyclization pathways. Accordingly, we have investigated the behavior of *o*-nitro-ketoximes with the CO/Fp^*_2 reductive system and report herein their novel conversion to 1*H*-indazoles.

RESULTS AND DISCUSSION

When 2-nitroacetophenone oxime **(1a)** was heated with 10 mol% of pentamethylcyclopentadienyl dicarbonyl iron(II) dimer $[Cp^*Fe(CO)_2]_2$ in dioxane under 50 atm CO, two main products were isolated: 3-methyl–1*H*-indazole (**2a**, 59 % yield) and 2-aminoacetophenone (**3a**, 15 %), identified spectroscopically and by comparison with authentic samples (eq. 1). Small amounts of other unidentified products and some tar were also produced. Reactions conducted at lower temperatures and pressures were extremely sluggish. Attempts to suppress the formation of ketone **3a** by the addition of drying agents (4Å molecular sieves, MgO, BaO) to the reactions were unsuccessful; no change in the **2a**/**3a** ratio was found. This suggests that the ketone byproduct is not the result of oxime hydrolysis but may derive from O-transfer from the oxime or nitro functions.



(1)

We have used this method to prepare several other 1*H*-indazoles as shown in Table 1. Substrates were chosen bearing both electron-donating (ED) and electron-withdrawing (EW) substituents. The 4',5'-

dimethoxy-2'-nitroacetophenone oxime (**1c**) gave the highest yield (**2c**, 85%). While substitution of the R group of the oxime had little effect for alkyl or aryl groups, trifluoromethyl substitution gave a poorer yield (**2b**, 40%). The higher yield with the substrate bearing ED groups is somewhat surprising given that more electron rich species should be harder to reduce. Indazoles with electron donating groups are more difficult to prepare by previous methods and therefore our route is complimentary.[18] The geometry of the oxime has little or no effect on the rate or the outcome of the cyclization, as suggested by the fact that the reactions of *E*-**1c** and *E*/*Z*-**1c** gave nearly identical product mixtures during the same reaction time.

Table 1. Synthesis of 1H-indazoles from *o*-nitroketoximes

1	R	X_1	X_2	Yield (%) **2**	Yield (%) **3**[a]	Time(h)
a	Me	H	H	59	15	46
b	CF_3	H	H	40[b]	--	72
c	Me	OMe	OMe	85	--	68
d	Ph	H	H	52	17	75
e	*p*-MeO-C_6H_4	H	H	56	--	75

a) Compound **3** was detected by GCMS in all cases, but due to separation difficulties was not always isolated. b) Yield based on recovered starting material.

Although the mechanism of this transformation is not yet known, it formally involves the removal of three oxygen atoms from the *o*-nitro-ketoxime. Although both the nitro- and oxime-functions are deoxygenated, presumably by O-transfer to coordinated CO ($\rightarrow CO_2$), the order of these steps and the nature of the intermediate which undergoes N-N bond formation are uncertain. Transition metal carbonyls are known to react with oximes to form imine and imine oxide complexes, which might be intermediates.[19] The imine (free or coordinated) or a derived iminyl radical[20] could then N-couple with the nearby nitroso group[21] (free or coordinated) to form the nitrogen-nitrogen bond (with subsequent deoxygenation). Efforts are currently underway to elucidate the mechanistic details of this remarkable transformation.

EXPERIMENTAL

All reactants and reagents were purchased from US suppliers unless otherwise noted. NMR spectra were recorded on Varian Mercury 300 or Gemini 400 spectrometers using residual solvent protons as references for all ^{13}C and ^{1}H spectra and $CFCl_3$ as an internal standard for ^{19}F NMR. TLC was performed on glass-backed plates (Sorbtech) and visualized with UV light. Flash chromatography was carried out on Kieselgel 60 (Merck). Elemental analysis was performed by Midwest Microlabs (Indianapolis, IN). The configuration of the oximes was determined by comparison of the ^{13}C NMR resonances of the methyl groups of the two isomers.[22] The following compounds were prepared by reported procedures: $[Cp^*Fe(CO)_2]_2$[23] (**1a**),[24] 4',5'-dimethoxy-2'-nitroacetophenone,[25] 2-nitrobenzhydryl[26] and MnO_2.[27]

2,2,2-Trifluoro-2'-nitroacetophenone oxime (1b). Applying the method of Knochel,[28] phenylmagnesium chloride (13.2 mL, 2.0M in THF) was added to a solution of 1-iodo-2-nitrobenzene (6.0 g, 24.0 mmol) in THF (40 mL) at –40ºC. After 5 min trifluoroacetic anhydride (4.23 mL, 30.0 mmol) was added dropwise. The mixture was stirred for 1 h at –40 ºC, quenched with saturated NH_4Cl (60 mL), and extracted with ether (4 x 30 mL). The ether extracts were combined and dried over $MgSO_4$, concentrated and then chromatographed on SiO_2 (1:4 ether/hexane), giving 2.34 g (45 %) of 2,2,2-trifluoro-2'-nitroacetophenone.[28] (Rf = 0.3). ^{1}H NMR (300 MHz, acetone-d_6) 7.83 (d, J = 6.6 Hz, 1H), 8.05- 8.12 (m, 2 H), 8.45 (d, J = 7.2 Hz, 1 H), ^{13}C NMR (75.45 MHz, acetone-d_6) 116.0 (q, $^{1}J_{CF}$ = 302 Hz), 125.0, 129.8, 129.9, 133.9, 136.2, 184.3 (q, $^{2}J_{CF}$ = 39 Hz).

The 2,2,2-trifluoro-2'-nitroacetophenone (800 mg, 3.65 mmol) was then refluxed in ethanol (10 mL) and pyridine (20 mL) with hydroxylamine hydrochloride (650 mg, 9.0 mmol) for 91 h. Solvent was removed *in vacuo* and the residue chromatographed on SiO_2 (1:5 ether/hexanes) to give 445 mg (52 %) of **1b** as a single isomer of undetermined stereochemistry. R_f = 0.35, mp 83-90 ºC; ^{1}H NMR (300 MHz acetone-d_6) 7.59 (1H, d, J = 7.2 Hz), 7.85 (1H, dt, J = 7.6 Hz, J = 1.5 Hz), 7.95 (1H, dt, J = 7.5 Hz, J = 1.5 Hz), 8.29 (1H, dd, J = 8.4 Hz, J = 0.9Hz), 12.02 (1H, br s); ^{13}C NMR (75.45 MHz, acetone-d_6) 121.3 (q, $^{1}J_{CF}$ = 272 Hz), 125.5, 130.7, 132.4, 135.1, 144.9 (q, $^{2}J_{CF}$ = 34 Hz), 148.7; ^{19}F NMR (282.35 MHz $CDCl_3$) -67.24. MS(EI) 186 (100), 167 (8), 138 (21), 63 (4). Exact Mass (ESI) calcd for $C_8H_5N_2O_3F_3Na$ (M+ Na) 257.0151, found 257.0157.

4',5'-Dimethoxy-2'-nitroacetophenone oxime (1c). To a solution of 4',5'-dimethoxy-2'-nitroacetophenone[25] (600 mg, 2.67 mmol) in pyridine (5 mL) and ethanol (10 mL) was added hydroxylamine hydrochloride (1.0 g, excess). The mixture was refluxed for 7 h and solvent was removed in vacuo. The residue was dissolved in $CHCl_3$ (30 mL) and washed with 2M HCl (3 x 20 mL). $CHCl_3$ was removed in vacuo to give **1c** as a light yellow solid. Recrystallization from a minimal

amount of hot ethanol gave 150 mg of yellow crystals that were the pure E isomer, mp 171-172 ºC. The supernatant liquid gave 470 mg of a mixture of isomers whose ratio was determined to be 5:3 (*E*:*Z*) by ^{1}H NMR, for a total yield of 620 mg (98 %, 72% *E*, 28% *Z*) MS(EI) 241 (18), 209 (100), 194 (25), 180 (10), 164 (24), 150 (46); *E* isomer IR (KBr) 3448, 2965, 2556, 1524, 1319 ^{1}H NMR (300 MHz, acetone-d_6) 2.12 (s, 3 H), 3.94 (s, 3 H), 3.95 (s, 3 H), 6.99 (s, 1 H), 7.57 (s, 1 H), 10.30 (s, 1 H); ^{13}C NMR (75.45 MHz, acetone-d_6) 15.4, 56.5, 56.7, 108.2, 112.9, 128.6, 141.3, 149.6, 153.7, 154.2. Anal. Calcd for $C_{10}H_{12}N_2O_5$: C 50.00, H 5.03, N 11.66. Found C 49.72, H 5.01, N 11.39. *Z* isomer: ^{1}H NMR (300 MHz, acetone-d_6) 2.18 (s, 3H), 3.97 (s, 3 H), 3.98 (s, 3 H), 6.89 (s, 1 H), 7.63 (s, 1 H), 9.69 (s, 1 H); ^{13}C NMR (75.45 MHz, acetone-d_6) 21.0, 56.5, 56.7, 107.8, 110.8, 126.4, 140.4, 149.2, 151.9, 154.4.

2-Nitrobenzophenone oxime (1d). A solution of 2-nitrobenzhydryl (723 mg, 3.2 mmol) in CH_2Cl_2 (15 mL) was refluxed with 1.6 g of MnO_2[28] for 20 h. The solution was filtered through Celite to give 674 mg (93%) of 2-nitrobenzophenone as yellow solid. mp 104-106 ºC, lit.,[29] mp 105-106 ºC. The 2-nitrobenzophenone (650 mg, 2.86 mmol) was refluxed in pyridine/ethanol (1:2 / 20 mL) for 30 h. Solvent was removed in vacuo and the residue was dissolved in ether and washed with 2M HCl (2 x 20 mL). The ether extract was concentrated and chromatographed on SiO_2 with $CHCl_3$/MeOH (35:1) to give 510 mg (2.10 mmol, 73%) of **1d** as a white solid along with 140 mg of recovered starting material. mp 117-121ºC, lit.,[22] mp 122-123ºC.

(4-Methoxyphenyl)(2-nitrophenyl)methanone oxime (1e). Applying the method of Knochel,[27] phenylmagnesium chloride (4.4 mL, 2.0 M in THF) was added to a solution of 1-iodo-2-nitrobenzene (2.0 g, 8.0 mmol) in THF (40 mL) at –40 ºC. After 5 min *p*-anisaldehyde (1.2 mL, 10.0 mmol) was added dropwise over 5 minutes. The mixture was stirred for 1 h at –40 ºC, quenched with saturated NH_4Cl (60 mL), and extracted with ether (4 x 30 mL). The ether extracts were combined and dried over $MgSO_4$, concentrated, and then chromatographed on SiO_2 (35% ether/hexane), giving 1.64 g (79%) of (4-methoxyphenyl)(2-nitrophenyl)methanol[30] as a yellow oil. Rf = 0.28. ^{1}H NMR (400 MHz, acetone-d_6) 3.75 (s, 3H), 5.14 (s, 1H), 6.41 (s, 1H), 6.86 (d, J = 6.6 Hz, 2H), 7.24 (d, J = 6.6 Hz, 2 H), 7.51 (t, J = 6.3 Hz, 1 H), 7.73 (t, J = 5.7 Hz, 1 H), 7.87 (dd, J = 6.0 Hz, J = 0.9 Hz, 1 H), 7.95 (d, J = 6.0 Hz). ^{13}C NMR (100.57 MHz, acetone-d_6) 55.5, 70.7, 114.4, 124.9, 129.0, 129.3, 129.6, 133.8, 136.2, 140.4, 149.4, 160.0.

The resulting (4-methoxyphenyl)(2-nitrophenyl)methanol (1.64 g, 6.33 mmol) and 1.23 g of MnO_2[22] were heated to reflux in CH_2Cl_2 (35 mL). After 23 h the reaction was only 40% complete (^{1}H NMR) so the mixture was then refluxed for 24 h more with an additional 3.0 g of MnO_2. The mixture was filtered through Celite and evaporated to give an orange solid that was dissolved in a minimal amount of hot

ether and recrystallized at 0 ºC to give 1.41 g (87 %) of (4-methoxyphenyl)(2-nitrophenyl)methanone as rose-colored crystals. mp 106-107ºC, lit.,[31] mp 86-90ºC; ^{1}H NMR (300 MHz, CD_3OD) 3.87 (s, 3H), 7.01 (d, J = 9.0 Hz, 2H), 7.51 (dd, J = 7.5 Hz, J = 1.5 Hz, 1H), 7.72 (d, J = 9.0 Hz), 7.76 (dd, J = 8.1 Hz, J = 1.5 Hz, 1H), 7.85 (dt, J = 7.5 Hz, J = 1.2 Hz), 8.24 (dd, J = 8.1 Hz, J =1.2 Hz, 1 H); ^{13}C NMR (100.57 MHz, CD_3OD) 56.3, 115.3, 125.8, 130.2, 130.3, 132.0, 133.1, 135.5, 137.6, 148.4, 166.1, 194.4.

To a solution of (4-methoxyphenyl)(2-nitrophenyl)methanone (1.31 g, 5.06 mmol) in pyridine/ethanol (20 mL 1:1) was added 2.0 g of hydroxylamine hydrochloride. The mixture was refluxed for 40 h. Solvent was removed in vacuo and the residue was dissolved in ether and washed with 2M HCl (2 x 20 mL). The ether extract was dried with $MgSO_4$ to give 1.31 g (95 %) of a yellow solid that was the oxime **1e**, mp 142-148 ºC. The ratio of *E/Z* isomers was determined by ^{1}H NMR spectroscopy to be 5:1. Recrystallization from ethanol gave the pure *E*-isomer. IR (KBr) 3228, 1607, 1529, 1262, ^{1}H NMR (300 MHz, acetone-d_6), 3.82 (s, 3H), 6.92 (d, J = 9.0 Hz, 2H), 7.36 (dd, J = 7.5 Hz, J = 1.5 Hz, 1 H), 7.44 (d, J = 9.0Hz, 2H), 7.74 (dt, J = 7.5 Hz, J = 1.5 Hz, 1H), 7.86 (dt, J = 7.5 Hz, J = 1.2 Hz, 1H), 10.43 (s, 1H), 8.20 (dd, J = 8.1Hz, J = 1.2Hz, 1H); ^{13}C NMR (100.57 MHz, acetone-d_6) 55.0, 114.0, 124.2, 128.1, 128.4, 129.8, 130.0, 130.7, 133.9, 148.8, 153.2, 161.0 MS (EI) 272 (M+, 53), 242 (8), 225 (27), 211 (15), 196 (22), 182 (100), 167 (53), 154 (85), 139 (19), 77 (24), 63 (21). Anal. Calcd for $C_{14}H_{12}N_2O_4$: C 61.76, H 4.44, N 10.29. Found: C 61.74, H 4.46, N 10.12. *Z*-isomer (oil), ^{1}H NMR (300 MHz, acetone-d_6) 3.90 (s, 3H), 10.83 (s, 1H).

3-Methyl-1*H*-indazole (2a). In a glass-lined, stainless steel Parr reaction vessel 2-nitro-acetophenone oxime (**1a**, 200 mg, 1.11 mmol) and $[Cp^*Fe(CO)_2]_2$ (54 mg, 0.11 mmol) were combined with dry dioxane (40 mL). The vessel was flushed three times with CO and charged to 50 atm (Caution: FUME HOOD!). The mixture was heated at 150 ºC for 46 h. The vessel was cooled to room temperature and the pressure was discharged (FUME HOOD!). The resulting brown solution was concentrated by rotary evaporation and then chromatographed on silica gel with a gradient elution of ether/hexanes (1:1 to 4:1) giving 86 mg of **2a** (59%) as a light brown solid, mp.110-114 ºC, lit.,[32] 110-112 ºC; Rf (1:1 ether/hexanes) = 0.29. Also isolated was 2-amino-acetophenone 22 mg (15%) which was spectroscopically identical to a commercial sample.

3-Trifluoromethyl-1*H*-indazole (2b). In the manner described for **2a**, 300 mg (1.28 mmol) of the oxime **(1b**) was combined with $[Cp^*Fe(CO)_2]_2$ (60 mg, 0.13 mmol) in dioxane (60 mL) and charged to 50 atm with CO. After heating at 150 ºC for 72 h, cooling, and solvent evaporation, the mixture was purified by preparative TLC with (30% EtOAc/hexanes) to give the indazole (**2b**) that was slightly

contaminated with a product of the same Rf, along with 72 mg (0.31 mmol) of recovered **1b**. Indazole (**2b)** was purified by preparative TLC, eluting with $CHCl_3$/MeOH (30:1) to give 72 mg (30 %) of **2b**. R_f ($CHCl_3$/MeOH) = 0.54, mp 73-78ºC, lit.,[33] mp 104ºC. Sublimation of this material at 100 ºC (0.1 mm Hg) gave a white powder, mp 94-97 ºC. ^{1}H NMR (300 MHz, acetone-d_6) 7.35 (t, J = 7.2 Hz), 7.52 (t, J = 6.0 Hz, 1 H), 7.75 (d, J = 8.4 H, 1H), 7.85 (d, J= 8.0 Hz), 13.2 (br s, 1 H). ^{13}C NMR (75.45 MHz, acetone-d_6) 111.9, 119.9, 120.2, 123.4 (q, $^1J_{CF}$ = 268 Hz), 123.7, 128.3, 135.2 (q, $^2J_{CF}$ = 38 Hz), 142.1. ^{19}F NMR (282.35 MHz $CDCl_3$) -61.67; MS (EI) 186 (100), 167 (8), 138 (20), 63 (4).

5,6-Dimethoxy-3-methyl-1*H*-indazole (2c). As above, 240 mg (1.00 mmol) of the oxime (**1c**) and 49 mg (0.10 mmol) of $[Cp^*Fe(CO)_2]_2$ in dioxane (60 mL) was heated at 150 ºC for 68 h. After cooling and solvent evaporation chromatography of the residue on silca gel with ethyl acetate/hexanes (4:1) gave 163 mg (0.85 mmol, 85%) of **2c** as a yellow solid that could be recrystallized from cold ether to give light brown crystals. R_f = 0.30; mp 163-167 ºC lit.,[18] mp 164 ºC; ^{1}H NMR (400 MHz, acetone-d_6) 2.45 (s, 3 H), 3.84 (s, 3 H), 3.85 (s, 3H), 6.96 (s, 1 H), 7.10 (s, 1H), 11.54 (br s, 1 H). ^{13}C NMR (100.57 MHz, acetone-d_6) 12.1, 56.1, 56.4, 92.5, 101.1, 116.5, 138.0, 141.8, 146.8, 152.0; MS(EI) 192 (100), 177 (64), 149 (24), 134 (17), 108 (22), 80 (13).

3-Phenyl-1*H*-indazole (2d). The oxime (**1e**) (294 mg, 1.21 mmol) with $[Cp^*Fe(CO)_2]_2$ (60 mg, 0.12 mmol) was heated at 150 ºC under 50 atm CO in dioxane (70 mL) for 75 h. After concentration, chromatography of the residue on silica gel with 30% ethyl acetate/hexanes gave 3-phenylindazole (**2d,** 0.63 mmol, 52 %). R_f = 0.30. mp 102-108 ºC, lit.,[32] mp 107-108 **°**C; the ^{13}C NMR spectra was identical to that described in the literature.[35] Also recovered was 2-aminobenzophenone, 40 mg (17%), identical spectroscopically to an authentic sample.

3-(4-Methoxyphenyl)-1*H*-indazole[35] **(2e).** The oxime (**1e**) (305 mg, 1.12 mmol) together with $[Cp^*Fe(CO)_2]_2$ (55 mg, 0.11 mmol) was heated at 150 ºC under 50 atm. CO in dioxane (70 mL) for 75 h. After concentration, chromatography of the residue on silica gel with $CHCl_3$/methanol (30:1) gave **2e** that was slightly impure. Preparative TLC of this mixture with CH_2Cl_2/acetone (95:5) gave 140 mg of **2e** (56 %) as a yellow gum. Rf (CH_2Cl_2/acetone) = 0.43; ^{1}H NMR (300 MHz, CD_3CN) 3.92 (s, 3H), 7.16 (d, J = 9.0 Hz, 2H), 7.30 (dt, J = 6.5 Hz, J = 0.9Hz, 1H), 7.50 (dt, J = 7.8Hz, J = 1.2Hz), 7.66 (d, J = 9.0 Hz, 1H), 8.02 (d, J = 9.0 Hz, 2H), 8.10 (d, J = 8.1Hz, 1H), 11.62 (br s, 1 H). MS (EI) 224 (100), 209 (62), 181 (30), 152 (20).

ACKNOWLEDGMENTS

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