A Facile Synthesis of Anthranilic Acid-Derived *N,N,O*-Terdentates

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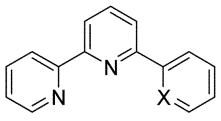
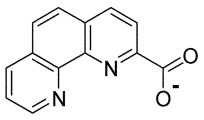
A plethora of efforts have been devoted to the study of photophysical, photochemical, biochemical as well as electrochemical properties of metal (such as ruthenium and osmium) complexes of 2,2';6',2"-terpyridine (**1a**, tpy) as the probes for studying photoinduced electron transfer and photosynthesis.[1] Studies on the properties of d_6-metal complexes of tpy are somewhat limited compared to those of 2,2-bipyridine due to limitations such as loss of ability to form chiral metal complexes and short excited state life time at the room temperature. Efforts to overcome such disadvantages prompted to study related terdentates such as 6-phenyl-2,2'-bipyridine (**1b**) as an *N,N,C*-terdentate analogue of tpy, which underwent cyclometallation to show some intriguing properties.[2]

Although the potential of 1,10-phenthroline-2-carboxylate (**2**) as an *N,N,O*-terdentate was studied four decades ago,[3] only very limited numbers of *N,N,O*-terdentate such as 2,2-bipyridine-2-carboxylate anion (**3**)[4] and *N*-(quinol-8-yl)-anthranilate anion (**4**)[5] were reported.



1a X = CH (tpy)
b X = N



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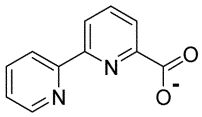

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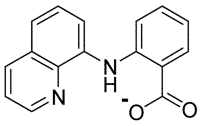

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Even though *N*-(2-aminoethyl)anthranilic acid (**6a**) could be a good candidate for *N,N,O*-terdentate, studies on this molecule have been focused on the application towards synthesis of EDTA family.[6]

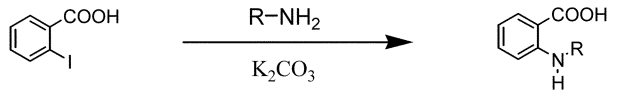
As a part of our studies on the *N,N,O*-terdentates and their metal complexes, we have been interested in *N*-(ω-aminoalkyl)-, *N*-(azaheteroaryl)- and *N*-(azaheteroarylalkyl)-anthranilic acids and have found that only very limited synthetic attempts were taken. Michael addition of anthranilic aicd to nitroethene, followed by catalytic hydrogenation,[7] direct alkylation of either anthranilic acid or alkyl anthranilate with 1,ω-dibromoalkane,[8] imine formation of anthranilic acid with aldehydes, followed reduction,[9] reaction of isatoic anhydride with 1,ω-diaminalkane, followed by hydrolysis,[10] and reaction of anthranilic acid with aziridine,[11] have been employed. These methods, however, were suffered from low yield, lack of availability of starting materials, severe reaction conditions, and sometimes formation of bis-products.

Ullmann-type arylamination has been the reaction of choice for the preparation of anthranilic acid derivatives since the discovery in 1903.[12] However, low yields presumably due to high reaction temperature somewhat limited the synthetic scope of this reaction.[13] Considerable amount of efforts to overcome such limitations have been pursued to find more efficient catalyst(s) which can catalyze under relatively mild conditions.[14]

Our preliminary studies to prepare *N*-(ω-aminoalkyl)-anthranilic acids from 2-chloro- and 2-bromobenzoic acid in the presence of Cu powder or copper salts were suffered by low yield, as expected.[15] Such low yields (more likely lower than 40%) have also been reported especially in the cases for the preparation of potential *N,N*-bidentates with anthranilic acid moiety as a part.[16] We reasoned that more reactive 2-iodobenzoic acid might undergo Ullmann-type arylamination without metal catalyst. However, somewhat surprisingly to us, only very limited numbers of such aminations of 2-iodobenzoic acid have been pursued and such cases have only been limited to the cases employing classical as well as designed catalyst.[14] Although literature study allowed us to find a patent wherein aminations of 2-iodobenzoic acid with ethylenediamine and 1,3-diaminopropane in presence of K_2CO_3 were described,[17] to the best of our knowledge, the Ullmann reactions under the same reaction condition were not pursued as yet.

We herein described a facile synthesis of *N*-(ω-aminoalkyl)-, *N*-(azaheteroaryl)-, and *N*-(azaheteroarylalkyl)-anthranilic acids by employing classical Ullmann reaction. The mixtures of 2-iodobenzoic acid in 1,ω-diaminoalkanes (~40 equiv.) (entry 1, 3, 4, 5) were heated at 100 °C for 8-12 h in the presence of K_2CO_3 (3 equiv.) to give the desired compounds in 65-87% yields (Table 1). The relatively low yield for **6c** is presumably due to the unfavorable interaction of the longer 4-amino-*n*-butyl chain. The reaction also pursued employing isoamyl alcohol as a solvent (entry 2, 6, 7, 8) with 1.2 equivalents of amines. Although isoamyl alcohol was employed as a solvent even when not needed

Table 1. Properties of *N*-Substituted Anthranilic Acids



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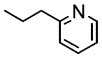
Entry (Compound)	R	Method	Yield (%)[a]	mp (°C) /lit. mp.
1 (**6a**[b])	$CH_2CH_2NH_2$	A	85	253-254 (245-246[8])
2 (**6a**[b])	$CH_2CH_2NH_2$	B	83	253-254
3 (**6b**[b])	$CH_2CH_2CH_2NH_2$	A	78	235-236
4 (**6c**[b])	$CH_2CH_2CH_2CH_2NH_2$	A	65	202-203
5 (**6d**)		A	87	153-154 (150-152[9])
6 (**6d**)		B	91	152-153
7 (**6e**)		B	82	157-158
8 (**6f**)		B	75	266-267 (266-267[16])

[a]Isolated, but not optimized yield. [b]Isolated as a HCl salt.

(entry 2, 6), the presence of solvent did not seem to affect the reactions very much compared to those done without solvent.

In conclusion, a series of *N*-(ω-aminoalkyl)-, *N*-(aza-heteroaryl)-, and *N*-(azaheteroarylalkyl)anthranilic acids were prepared as potential *N,N,O*-terdentates by reacting 2-iodobenzoic aid with appropriate amines in the presence K_2CO_3 without any additional catalyst.

Experimental Section

Melting points were determined using a Fischer-Jones melting points apparatus and are not corrected. IR spectra were obtained using a Perkin-Elmer 1330 spectrophotometer. NMR spectra were obtained using a Bruker-250 spectrometer 250 MHz or 400 MHz for ^{1}H NMR and 62.5 MHz or 100 MHz for ^{13}C NMR and are reported as parts per million (ppm) from the internal standard tetramethylsilane (TMS). Chemicals and solvents were commercial reagent grade and used without further purification. Elemental analyses were taken on a Hewlett-Packard Model 185B elemental analyzer.

***N*-(2-Aminoethyl)anthranilic Acid (General Method). Method A:** A mixture of ethylenediamine (20 g, 330 mmol), 2-iodobenzoic acid (2.06 g, 8.30 mmol), and K_2CO_3 (3.40 g, 25 mmol) was heated at 100 °C for 8-12 h. To reaction mixture was added 30 mL of water. Evaporation of solvent *in vacuo* afforded a pale brown solid, which was redissolved in 30 mL of water and filtered off insoluble material, if any. The filtrate was carefully made acidic (pH = ~3) with conc. HCl. The precipitate formed was collected and washed with water followed by cold methanol to give 1.19 g of product. Cooling the filtrate afforded an additional 0.25 g of product (85%) as **6a**·2HCl: mp 253-254 °C (lit.[6] mp 245-246 °C). Unreported spectral data are as follows: IR (KBr) υ 3334.5, 3022.3, 1660.6, 1574.5, 1512.7, 1430.8, 1320.2, 1256.7, 1220.7, 1165.5, 1150.0, 1012.5, 750.5, 745.2 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.6 (br s, COOH), 8.31 (br s, NH), 7.89 (d, J = 7.4 Hz, H3), 7.34 (t, J = 6.8 Hz, 7H, H4), 6.87 (d, J = 8.2 Hz, H6), 6.59 (t, J = 6.8 Hz, H5), 3.56 (br s, 2H), 2.94 (br s, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 169.8, 150.2, 134.5, 131.8, 114.8, 110.9, 39.5, 37.5.

Method B: A mixture of ethylenediamine (60.8 mg, 9.96 mmol), 2-iodobenzoic acid (2.06 g, 8.30 mmol), and K_2CO_3 (3.40 g, 25 mmol) in 25 mL of isoamyl alohol was heated at 100 °C for 8-12 h. Work up as described above for method A afforded 1.40 g (83%) of white needles: mp 253-254 °C.

***N*-(3-Aminopropyl)anthranilic Acid (6b)·HCl.** White needles (CH_3OH). Unreported spectral data are as follows: IR (KBr) υ 3336.5, 3020.5, 1660.6, 1575.4, 1515.3, 1432.1, 1320.1, 1257.0, 1165.44, 1150.5, 1012.5, 754.5, 745.7 cm^{-1}. ^{1}H NMR (D_2O, 400 MHz) δ 8.00 (dd, J = 8.4, 1.6 Hz, H6), 7.58 (ddd, J = 8.4, 8.0, 1.6 Hz, H4), 7.20-7.15 (m, 2H), 3.38 (t, J = 7.6 Hz, 2H), 3.01 (t, J = 7.6 Hz, 2H), 2.00 (quintet, J = 7.6 Hz, 2H). ^{13}C NMR (D_2O + CH_3OH, 100 MHz) δ 171.7, 139.7, 138.3, 135.5, 131.9, 125.9, 124.1, 39.5, 27.6, 26.7.

***N*-(4-Aminobutyl)anthranilic Acid (6c)·HCl.** White platelets (CH_3OH): IR (KBr) υ 3403.5, 3020.5, 1660.2, 1574.5, 1519.3, 1430.1, 1322.1, 1257.0, 1223.1, 1165.0, 1151.6, 1011.5, 753.5, 744.5 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.06 (dd, J = 8.0, 1.6 Hz, H6), 7.65 (td, J = 8.0, 1.6 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.42 (d, J = 7.6, 1.2 Hz, H3), 3.38 (t, J = 6.8 Hz, 2H), 2.94 (t, J = 6.8 Hz, 2H), 1.77-1.70 (br. s, 4H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 170.77, 150.56, 131.69, 128.51, 127.55, 113.74, 110.65, 41.62, 38.44, 25.79, 24.93. Anal cal for $C_{11}H_{17}N_2O_2Cl0.5H_2O$: C, 52.07; H, 7.15; N, 11.05. Found: C, 52.03; H, 7.18; N, 10.97.

***N*-(Pyridin-2-ylmethyl)anthranilic Acid (6d)·HCl.** White needles (CH_3OH): Unreported spectral data are as follows: IR (KBr) υ 3335.7, 3020, 1659.6, 1575.8, 1517.3, 1431.8, 1321.5, 1257.0, 1221.7, 1164.5, 1150.6, 1012.5, 754.5, 745.7 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.64 (br s, COOH), 8.55 (dd, J = 4.8, 1.2 Hz, H6'), 7.82 (dd, J = 8.0, 1.6 Hz, H3'), 7.74 (ddd, J = 8.0, 7.8, 1.6 Hz, H4'), 7.35 (d, J = 8.0 Hz, H6), 7.30 (ddd, J = 8.2, 8.0, 1.6 Hz, H4), 7.26 (dd, J = 8.0, 4.8 Hz, H5'), 6.65 (d, J = 8.4 Hz, H3), 6.56 (ddd, J = 8.2, 8.0, 1.0 Hz, H5), 4.54 (s, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 169.79, 158.36, 150.41, 149.03, 136.81, 134.38, 131.72, 122.21, 121.30, 114.54, 111.62, 110.51, 47.71.

***N*-[2-(Pyridin-2-yl)ethyl]anthranilic Acid (6e)·HCl.** White needles (CH_3OH): IR (KBr) υ 3340.5, 3010.2, 1660.2, 1576.5, 1518.3, 1432.3, 1320.5, 1257.6, 1221.0, 1165.0, 1151.6, 1012.2, 750.5, 743.7 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.56 (d, J = 4.0 Hz, H6'), 7.81 (d, J = 8.0, 1.2 Hz, H3'), 7.74 (d, J = 8.0, 1.8 Ha, H4'), 7.40 (ddd, J = 8.0, 7.8, 1.6 Hz, H4), 7.36 (d, J = 8.0 Hz, H6), 7.26 (dd, J = 7.6, 4.8 Hz, H5'), 6.83 (d, J = 8.4 Hz, H3), 6.59 (t, J = 8.0 Hz, H5), 3.60 (t, J = 6.8 Hz, 2H), 3.09 (t, J = 6.8 Hz, 2H).

^{13}C NMR (DMSO-d_6, 100 MHz) δ 169.88, 159.01, 150.68, 149.10, 136.50, 134.50, 131.69, 133.33, 121.58, 114.17, 111.12, 110.00, 41.89, 36.83. Anal cal for $C_{14}H_{14}N_2O_2H_2O$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.55; H, 6.17; N, 10.81.

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References And Notes

1. (a) Kalyanasundaram, K. *Photochemistry of Polypyridine and Phorphyrin Complexes*; Academic Press: San Diego, CA 1992. (b) Juris, A.; Balzani, V.; Barigelletti, F.; Campagna, S.; Belser, P.; von Zelewsky, A. *Coord. Chem. Rev.* **1988**, *84*, 85.
2. (a) Constable, E. C.; Henney, R. P. G.; Leese, T. A.; Tocher, D. A. *J. Chem. Soc. Dalton Trans.* **1990**, 443. (b) Collin, J. P.; Beley, M.; Sauvage, J. P.; Barigelletti, F. *Inorg. Chim. Acta* **1991**, *65*, 214. (c) Constable, E. C.; Cargill, T.; Alexander, M. W.; Greulich, S. *J. Chem. Soc. Chem. Comm.* **1995**, 3571.
3. Goodwin, H. A.; Sylva, R. N. *Aust. J. Chem.* **1967**, *20*, 217.
4. Norby, T.; Boerje, A.; Akermark, B.; Hammarstroem, L.; Alsins, J.; Lashgari, K.; Norrestam, R.; Martensson, J.; Stenhagen, G. *Inorg. Chem.* **1997**, *36*, 5850.
5. Steiner, E.; Schetty, G. *Helv. Chim. Acta* **1973**, *56*, 368.
6. (a) Sandhu, G. K.; Verma, S. P.; Moore, L. S.; Parish, R. V. *J. Orgometallic Chem.* **1986**, *315*, 309. (b) Young, A.; Sweet, T. R. *J. Am. Chem. Soc.* **1958**, *80*, 800.
7. Bachman, G. R.; Welton, D. E. *J. Org. Chem.* **1947**, *12*, 208.
8. Alphen, J. V. *Rec. Trav. Chim.* **1941**, *60*, 493.
9. Pitt, C. G.; Bao, Y.; Thompson, J.; Wani, M. C.; Rosenkrantz, H.; Metterville, J. *J. Med. Chem.* **1986**, *29*, 1231.
10. Clark, R. H.; Wagner, E. C. *J. Org. Chem.* **1944**, *9*, 55.
11. Wünsh, K. H.; Stahnke, K. H.; Gomoll, P. *Z. Chem.* **1970**, *6*, 219.
12. Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382.
13. For a review, see Lindley, J. *Tetrahderon* **1984**, *40*, 1433.
14. (a) Ma, D.; Cai, Q.; Zhang, H. *Org. Letters* **2003**, *5*, 2453, and references therein. (b) Kim, Y. M.; Yu, S. *J. Am. Chem. Soc.* **2003**, *125*, 1696. (c) Lin, G.; Hong, R. *J. Org. Chem.* **2001**, *66*, 2877. (d) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901. (e) Sanches, E.; Del Campo, C.; Avendano, C.; Llama, E. *Heterocycles* **1990**, *31*, 2003. (f) Miyano, S.; Fukushima, H.; Handa, S.; Ito, H.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3249. (g) Kaiser, C.; Fowler, P. J.; Tedesch, D. H.; Lester, B. M.; Garvey, E.; Zirkle, C. L.; Nodiff, E. A.; Saggiomo, A. J. *J. Med. Chem.* **1974**, *17*, 57.
15. Unpublished results.
16. Bongui, J.-B.; Elomri, A.; Seguin, E.; Tillequin, F.; Pfeiffer, B.; Penardo, P.; Pierre, A.; Atassi, G. *Chem. Pharm. Bull.* **2001**, *49*, 1077.
17. Inaba, T.; Okada, H.; Minami-ashigara, K. *DE 4222463 A1*, 1993.