

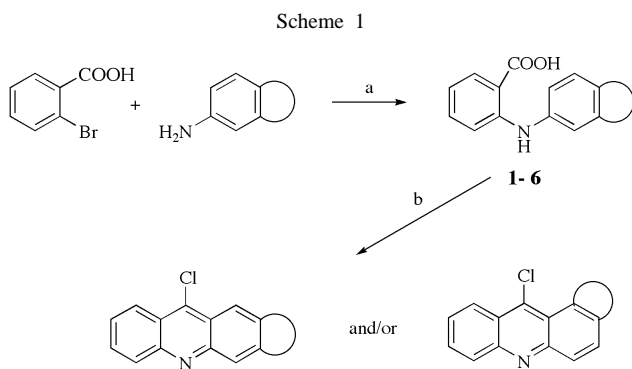
Maxime Robin,* Valérie Pique, Robert Faure and Jean-Pierre Galy

Laboratoire de Valorisation de la Chimie Fine, Faculté des Sciences et Techniques de Saint Jérôme, Université d'Aix-Marseille III, Av. Esc. Normandie-Niemen, 13397 Marseille Cedex 20, France.
Received February 20, 2002

The synthesis of *N*-aryl anthranilic acid derivatives bearing dioxolo, dioxino, cyclopent, and imidazolo supplementary ring systems is reported. The Ullmann-Goldberg condensation of the *N*-aryl anthranilic acid is improved in yield and reaction time, compared to conventional heating; by ultrasonic irradiation.

J. Heterocyclic Chem., **39**, 1083 (2002).

Natural tetracyclic alkaloid derivatives are involved in many fields including total synthesis and pharmacological activities. Because of the importance of acridine derivatives in clinical medicine [1] and the recent development of amsacrine-based compounds as anticancer drugs [2] and as a new class of antiprion compounds [3] we investigated the synthesis of some tetracyclic acridines bearing different supplementary heterocyclic ring systems, and their amsacrine derivatives. We are interested in the synthesis of tetracyclic acridine with a thiazolo supplementary ring system [4], and the synthesis of oxazolo[4,5-*b*]acridine derivatives [5]. In that case, we developed a method using ultrasonic irradiation (UI) to increase the Ullmann condensation in the synthesis of anthranilic acids used as intermediates, according to the acridine synthetic pathway shown in Scheme 1.



(a) Ultrasonic Irradiation (Trans-sonic 570/H at 35 Khz), 80 °C, Cu/Zn, K₂CO₃, butan-2-one; (b) POCl₃, 120 °C, 3 h.

To improve this method, we chose different acridine analogues already described with poor yields, and compared the classical Ullman-Jourdan condensation [6] with ultrasound. There are only few references on the synthesis of dioxolo [7], dioxino [8], cyclopent [9], and imidazolo acridine. In all these cases, the *N*-aryl anthranilic acids used as precursor for the synthesis of acridines are described with low yields. Usually, these compounds are prepared by the Ullmann-Goldberg condensation [10]. Our laboratory has prepared

different *N*-aryl anthranilic acids by ultrasonic irradiation with convenient yields for various heterocyclic compounds [11]. This method allows comparison of conventional Ullmann condensation and ultrasonic irradiation. Data collected in Table 1 confirm that UI is a powerful technique for the synthesis of anthranilic acid (**1-6**). UI of a solution gave the desired compound in yields similar to, and sometimes better than those obtained by conventional heating. The overall time was considerably reduced, the reactions were cleaner, and the products were easily purified.

Table 1
Comparison Between Conventional Heating and Ultrasonic Irradiation

Structure	Conventional heating [a]	Ultrasonic Irradiation [b]
 1	R=Cl, 25 %, 12 h.	86 %, 3 h. [4c]
	R=H, 24 %, 12 h. [4b]	72 %, 3 h.
	R=CH ₃ , 23 %, 12 h. [4b]	81 %, 3 h.
 2	21 %, 6 h. [7]	45 %, 3 h.
	42 %, 12 h. [12]	
 3	58 %, 3 h. [8]	81 %, 3 h.
	53 %, 12 h. [12]	
 4	33 %, 12 h. [9]	70 %, 3 h.
 5	51 %, 3 h. [13]	87 %, 3 h.
 6	Never done	90 %, 3 h. [5]

[a] Oil bath 110 °C, Cu, K₂CO₃, pentan-1-ol; [b] Ultrasonic Irradiation (Trans-sonic 570/H at 35 Khz), 80 °C, Cu/Zn, K₂CO₃, butan-2-one.

In conclusion, we have described the synthesis of *N*-aryl anthranilic acids carrying an extra fused ring, which are the key step intermediates in the synthesis of tetracyclic acridine derivatives [14]. The use of ultrasonic irradiation is an interesting technique in the synthesis of anthranilic acid. The extension of such experiments to other heterocycles is now being investigated.

EXPERIMENTAL

Reagents and solvents were purchased from common commercial suppliers. Melting points were determined with an Electrothermal 9300 apparatus and are uncorrected. The NMR spectra were recorded on a Bruker AC 200 spectrometer operating at 50.3 MHz for ^{13}C . 2D NMR spectra, both of homonuclear (COSY) and heteronuclear (HMBC, HMQC) correlations, were obtained with a Bruker AMX 400. In all cases TMS was used as an internal standard.

General Procedure for the Synthesis of Anthranilic Acids 1-6.

Just before starting the reaction, the copper catalyst was prepared from 0.8 g of anhydrous copper sulfate in 5 mL of water, to this solution was added 0.3 g of powdered zinc keeping the temperature almost constant. The copper/zinc precipitate was filtered, washed first with water, then with acetone and dried in the oven. In a 100 mL round bottom flask were placed a mixture of amino heterocycle (10 mmoles), 2.21 g of *o*-bromobenzoic acid (11 mmoles), 1.7 g of anhydrous potassium carbonate (12 mmoles), 0.06 g of powdered copper/zinc and 25 mL of butan-2-one. This mixture was sonicated in a bath (80 °C) for 3 hours. After evaporation of the solvent, the residue was stirred with 80 mL of hot water, filtered and acidified to pH 5 with 2N HCl. The new precipitate formed was collected by filtration, washed with water and dried to give 1-6. Spectral data for these compounds are consistent with the literature.

N-[(2-Chloro-benzothiazol-6-yl)amino]benzoic Acid (1).

Compound 1 was obtained in 86% yield, mp 186 °C, Mol. Wt.: 305; ^1H NMR (DMSO- d_6): δ 6.84 (t, 1H, $J=8.4$ Hz C-H $_{10}$), 7.31-7.47 (ma, 3H), 7.86-8.00 (ma, 3H), 9.80 (s, 1H, N-H $_7$); ^{13}C NMR (DMSO- d_6): δ 112.65* (C-7), 114.01* (C-9), 118.26 (C-11), 121.17 (C-5), 123.03 (C-4), 131.99 (C-12), 134.08 (C-10), 137.10 (C-7a), 139.14 (C-6), 146.02 (C-3a), 146.07 (C-8a), 150.38 (C-2), 169.91 (C-13), n.o. (C-12a). Anal. Calcd. for $\text{C}_{14}\text{H}_9\text{ClN}_2\text{O}_2\text{S}$: C, 55.12; H, 2.95; N, 9.19. Found: C, 55.32; H, 3.19; N, 8.95.

N-(1,3-Benzodioxol-5-ylamino)benzoic Acid (2).

Compound 5 was obtained in 45% yield, mp 170 °C, Mol. Wt.: 257; ^1H NMR (DMSO- d_6): δ 6.02 (bs, 2H, (CH $_2$) $_2$), 6.70 (m, 2H, C-H $_{6-11}$), 6.88 (m, 3H, C-H $_{4-7-9}$), 7.09 (ddd, 1H, C-H $_{10}$), 7.31 (d, 1H, C-H $_{12}$); ^{13}C NMR (DMSO- d_6): δ 101.24 (C-2), 105.28 (C-4), 108.61 (C-7), 111.57 (C-12a), 113.17 (C-6), 116.39 (C-9), 116.56 (C-11), 131.80 (C-12), 134.19 (C-10), 134.38 (C-5), 143.93 (C-7a), 147.98 (C-3a), 148.54 (C-8a), 170.00 (C-13).

Anal. Calcd. for $\text{C}_{14}\text{H}_{11}\text{NO}_4$: C, 65.37; H, 4.31; N, 5.44. Found: C, 65.32; H, 4.21; N, 5.25.

N-(2,3-Dihydro-1,4-benzodioxin-6-ylamino)benzoic Acid (3).

Compound 3 was obtained in 81% yield, mp 191 °C, Mol. Wt.: 271; ^1H NMR (DMSO- d_6): δ 4.22 (bs, 4H, 2(CH $_2$) $_{2,3}$), 6.73-6.86

(ma, 4H, C-H $_{5-7-8-12}$), 7.02 (d, 1H, C-H $_{10}$), 7.32 (ddd, 1H, C-H $_{11}$), 7.85 (d, 1H, C-H $_{13}$), 9.37 (bs, 1H, COOH); ^{13}C NMR (DMSO- d_6): δ 63.9 (C-2), 64.2 (C-3), 111.7 (C-13a), 111.9 (C-5), 113.1 (C-10), 116.3 (C-7), 116.5 (C-12), 117.6 (C-8), 131.8 (C-13), 133.7 (C-11), 134.2 (C-9a), 143.7 (C-4a; C-8a), 148.3 (C-6), 170.0 (C-14).

Anal. Calcd. for $\text{C}_{15}\text{H}_{13}\text{NO}_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.62; H, 4.91; N, 5.25.

N-(2,3-Dihydro-1H-inden-5-ylamino)benzoic Acid (4).

Compound 4 was obtained in 70% yield, mp 167 °C, Mol. Wt.: 253; ^1H NMR (DMSO- d_6): δ 2.00 (q, 2H, (CH $_2$) $_2$), 2.83 (m, 4H, (CH $_2$) $_{1-3}$), 6.70 (bs, 1H, C-H $_6$), 6.88 (m, 2H, C-H $_{4-7-9}$), 7.08 (d, 1H, C-H $_{10}$), 7.31 (ddd, 1H, C-H $_{12}$), 7.32 (d, 1H, C-H $_{11}$); ^{13}C NMR (DMSO- d_6): δ 25.2 (C-2), 31.73 (C-3), 32.73 (C-1), 112.0 (C-12a), 113.3 (C-9), 116.6 (C-11), 118.3 (C-4), 120.3 (C-6), 124.8 (C-7), 131.8 (C-12), 134.0 (C-10), 138.4 (C-7a), 138.9 (C-5), 145.1 (C-3a), 148.0 (C-8a), 169.8 (C-13).

Anal. Calcd. for $\text{C}_{16}\text{H}_{15}\text{NO}_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.52; H, 5.27; N, 5.55.

N-[(2-Chloro-1-methyl-1H-benzimidazol-5-yl)amino]benzoic Acid (5).

Compound 5 was obtained in 87% yield, mp: 226 °C, Mol. Wt.: 302; ^1H NMR (DMSO- d_6): δ 3.79 (s, 3H, (CH $_3$) $_{14}$), 6.71 (ddd, 1H, C-H $_{11}$), 7.01 (dd, 1H, C-H $_9$), 7.21 (dd, 1H, C-H $_6$), 7.32 (ddd, 1H, C-H $_{10}$), 7.45 (d, 1H, C-H $_4$), 7.59 (d, 1H, C-H $_7$), 7.88 (dd, 1H, C-H $_{12}$), 9.60 (bs, 1H, N-H $_8$); ^{13}C NMR (DMSO- d_6): δ 30.7 (C-14), 111.3 (C-7), 111.6 (C-12a), 112.9 (C-4), 113.0 (C-9), 116.7 (C-11), 119.9 (C-6), 131.8 (C-12), 132.9 (C-7a), 134.3 (C-10), 135.3 (C-5), 140.7 (C-2), 141.8 (C-3a), 148.7 (C-8a), 170.1 (C-13).

Anal. Calcd. for $\text{C}_{15}\text{H}_{12}\text{ClN}_3\text{O}_2$: C, 59.71; H, 4.01; N, 11.75. Found: C, 59.84; H, 4.12; N, 11.74.

N-[(2-(Dimethylamino)-benzoxazol-6-yl)amino]-benzoic acid (6).

Compound 6 was obtained in 90% yield, mp 224 °C, Mol. Wt.: 297; ^1H NMR (DMSO- d_6): δ 3.09 (s, 6H, 2 α CH $_3$), 6.67 (ddd, 1H, $J=1.1, 7.7$ Hz, C-H $_{11}$), 6.98 (m, 2H, C-H $_5$, C-H $_{10}$), 7.28 (m, 2H, C-H $_4$, C-H $_9$), 7.30 (s, 1H, C-H $_7$), 7.86 (dd, 1H, $J=7.7$ Hz, C-H $_{12}$), 9.54 (s, 1H, N-H $_8$); ^{13}C NMR (DMSO- d_6): δ 37.5 (C- α), 105.3 (C-4), 111.6 (C-12a), 113.2 (C-9), 115.8 (C-5), 116.7 (C-11), 120.2 (C-7), 132.0 (C-12), 133.3 (C-6), 134.5 (C-10), 140.5 (C-3a), 149.0 (C-7a), 149.3 (C-8a), 163.1 (C-2), 170.4 (C-13).

Anal. Calcd. for $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}_3$: C, 64.64; H, 5.09; N, 14.13. Found: C, 64.51; H, 5.10; N, 14.26.

REFERENCES AND NOTES

- [1] Albert, A. Selective Toxicity, 7th ed.; Chapman & Hall: London, 1985.
- [2] W. A. Denny, and B. C. Baguley, Molecular Aspects of Anti-Cancer Drug-DNA Interactions; S. Neidle and M. J. Waring, Eds.; Macmillan: London, 1994; pp 270-311.
- [3] C. Korth, B. C. H. May, F. E. Cohen and S. B. Prusiner, *Proc. Natl. Acad. Sci. USA*, **98**, 9836 (2001).
- [4a] I. B. Taraporewala, J. W. Cessac, T. C. Chanh, A. V. Delgado and R. F. Schinazi, *J. Med. Chem.*, **35**, 2744 (1992); [b] S. Morel, J.-P. Galy, J. Elguero and J. Barbe, *Tetrahedron Lett.*, **34**, 2609 (1993); [c] M. Robin, R. Faure, A. Périchaud and J.-P. Galy, *Heterocycles*, **53**, 387 (2000).

- [5] M. Robin, R. Faure, A. Périchaud and J-P. Galy, *Synth. Commun.*, **32**, 981 (2002).
- [6] March, J. *Advanced Organic Chemistry*, 4th Ed.; Wiley-Intersciences, New-York, 1992.
- [7] M. Kimura, I. Okabayashi and A. Kato, *J. Heterocyclic Chem.*, **29**, 73 (1992).
- [8] M. Kimura, I. Okabayashi and A. Kato, *J. Heterocyclic Chem.*, **30**, 1101 (1993).
- [9] S. Morel, F. Chatel, G. Boyer and J-P. Galy, *J. Chem. Research*, **4**, 115 (1998).
- [10] Acheson, R. M. "Acridines", Interscience Publishers, New-York, 1956, pp 160-171.
- [11] J.-P. Hanoun, J.-P. Galy and A. Tenaglia, *Synth. Commun.*, **25**, 2443 (1995).
- [12] S. Morel, J-P. Galy and R. Faure, *Magn. Reson. Chem.*, **35**, 556 (1997).
- [13] J-P. Galy, J-P. Hanoun, V. Pique, N. Jagerovic and J. Elguero, *J. Heterocyclic Chem.*, **34**, 1781 (1997).
- [14] M. Robin, J-P. Galy and R. Faure, *Magn. Reson. Chem.*, **39**, 225 (2001).