8th International Electronic Conference on Synthetic Organic Chemistry. ECSOC-8. 1-30 November 2004.
http://www.lugo.usc.es/~qoseijas/ECSOC-8/

[A014]

Synthesis of 1-amino-4-(2´-thienyl)phthalazine derivatives

M. Manuela M. Raposo*[a] Ana M. B. A. Sampaio[a] and G. Kirsch[b]

[a]Centro de Química, Universidade do Minho, Campus de Gualtar
4710-057 Braga, Portugal

[b]Laboratoire d´Ingénierie Moléculaire et Biochimie Pharmacologique,
UFR SciFA/Université de Metz 1, Boulevard Arago, Metz Technopôle,
57078 Metz Cedex 3, France

Abstract- A synthesis of 1-amino substituted 4-(2´-thienyl)-phthalazines is described from halo- derivatives of 4-(2´-thienyl)-1-(2*H*)-phthalazinone **3**.

Keywords: Friedel-Craft´s acylation, 1-amino-4-(2´-thienyl)phthalazines.

Introduction

The practical interest upon phthalazine derivatives is based on their widespread applications [1-4]. Phthalazines, like others members of the isomeric diazine series, have found wide applications as therapeutic agents [2], [5-21]. Phthalazines are also commonly used as ligands in transition metal catalysis [22-26], as chemiluminescent materials [27-31] and for optical applications [32].

Despite their significance, there are only a limited number of routes for the synthesis of phthalazines. The most commonly employed approach is through *o*-disubstituted benzenes. Thus, condensation of 1,2-diacylbenzenes or their aldehyde counterparts with hydrazine derivatives gives 1,4-disubstituted- or the parent unsubstituted phthalazines, respectively [1-3], [5-7], [9-10], [12]. Recently, palladium catalyzed coupling reactions were also applied in the phthalazine series [33-34]. Guery *et al* [33] obtained several new phthalazine derivatives through Suzuki coupling.

Due to the nature of the phthalazine nucleus, synthesis of new derivatives becomes an importante issue. There has been little reported in the literature concerning 4-thienyl substituted phthalazines [17-18], [35-36]. It was for that reason that we decide to synthesize new thienylphthalazine derivatives.

In this paper we report the synthesis of new 1-amino-4-(2´-thienyl)phthalazine derivatives **5a**-**e** from halo derivatives **4a**-**b** of the phthalazinone **3**. Compound **3** was

*Corresponding author. Phone: +351 253 604381: Fax: +351 253 678983: e-mail: mfox@quimica.uminho.pt

obtained by cyclization of acylbenzoate **2** using hydrazine hydrate. The latter was made through a Friedel-Crafts reaction between thiophene and phthalic acid monochloride ester **1**.

Results and Discussion

The 2-thienyl substituted benzoate **2** was obtained, in good yield (81%), by the standard method of Friedel-Crafts reaction of thiophene with *o*-phthalic acid monomethylester chloride **1**. This compound was subsequently cyclized by condensation with hydrazine hydrate to give phthalazinone **3** in 91% yield from benzoate **2** (Scheme 1, Table 1). Phthalazinone **3** was already synthesized by Buu-Hoï *et al* [36], by condensation of 2-(2´-thienyl)-2-oxo-benzoic acid with hydrazine hydrate.

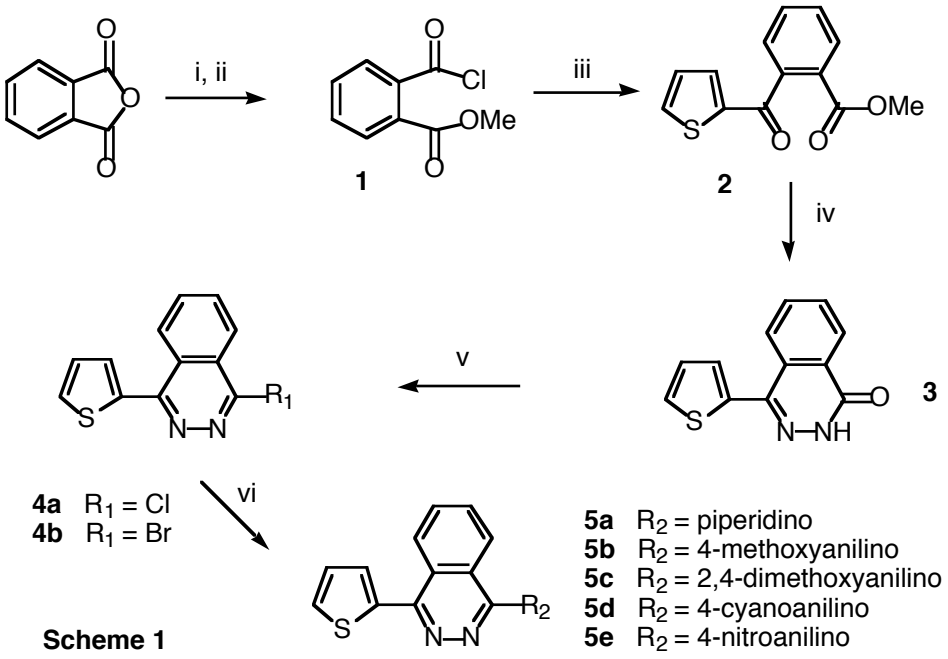
Bromine and chlorine substituted phthalazines play an important role in diazine chemistry since they offer the potential for further funtionalization. By nucleophilic displacement of the halogen group, numerous otherwise inaccessible diazines become available. To this end we have synthesized and characterized chloro- and bromo-phthalazine derivatives.

From **3**, bromo and chloro derivatives were prepared by reaction with phosphoryl halides. The chloride **4a** and the bromide **4b**, were obtained with respectively 99 and 87% yield. 1-Chloro-4-(2´-thienyl)-phthalazine **4a** has been already reported in a patent [35], by condensation of 1,4-dichlorophthalzine with thienyllithium. No data about the derivative are given.

Arylamino- and piperidinylphthalazine derivatives show anti malarial activity and are useful for treatment of septic shock, multi-organ failure, chronic rheumatoid arthritis, multiple sclerosis, SLE, AIDS, hepatitis, type-II diabetes etc. [20-21].

In order to synthesize several new 1-(alkyl)arylamino-4-(2´-thienyl)-phathazines, 1-chloro-4-(2´-thienyl)-phthalazine **4a** was reacted with an excess of piperidine or an excess of several arylamines, in refluxing acetone [37], for 3-15 h, to yield 1-(alkyl)arylamino-4-(2´-thienyl)-phathazines **5a-e** in moderate to good yields (47-84%) (Scheme 1, Table 1).

Compounds **2-5403 243.43999 Tm (l66-449 Tc 12 Tm (arthr)T 12 0 0 12 38em (l6hs 201 243.**



Scheme 1

Scheme 1. *Reagents and conditions*: i, MeOH, reflux; ii, $SOCl_2$, CH_2Cl_2, reflux; iii, thiophene, $SnCl_4$, CH_2Cl_2, 0 ºC; iv $NH_2NH_2.H_2O$, ethanol, reflux; v, POX_3 (X = Cl or Br), □; vi, amine, acetone, H_2O, HCl (conc.), reflux.

Table 1. Synthesis of compounds **2**-**5**.

Compound	R_1 or R_2	Yield (%)	IR □max [cm^{-1}]
2	-----	81	1724 (C=O) 1649 (C=O)
3	-----	91	3301 (NH), 1665 (C=O)
4a	R_1 = Cl	99	-----
4b	R_1 = Br	87	-----
5a	R_2 = piperidinylo	84	-----
5b	R_2 = 4-Methoxyanilino	47	3418 (NH)
5c	R_2 = 2,4- Dimethoxyanilino	52	3434 (NH)
5d	R_2 = 4-Cyanoanilino	62	3409 (NH) 2213 (CN)
5e	R_2 = 4-Nitroanilino	71	3281 (NH)

Experimental

General procedure for the synthesis of 1-(alkyl)arylamino-4-(2´-thienyl)-phthalazines **5a-e**.

Amine (2.43 mmol), water (0.017 mL) and one drop of HCl (37%) were added to a stirred solution of 1-chloro-4-(2´-thienyl)-phthalazine **4a** (4.2 g, 0.81 mmol) in acetone (20 mL). This mixture was heated at reflux for 3-15 h then cooled and the phthalazine chlorohydrate separated by filtration affording a pale brown solution. This organic solution was evaporated under reduced pressure to give a crude solid. This solid was dissolved in dichloromethane and the solution obtained was basified with a solution of ammonia (2 M), extracted with chloroform (3x30 mL) and washed with water (3x30 mL). The combined organic extracts were dried and the solvent was evaporated under reduced pressure to give the crude 1-(alkyl)aryl-4-(2´-thienyl)-phthalazines **5a**-**e** which were purified by recrystallization or by "flash" chromatography on silica with increasing amounts of ether in petrol ether (b.p. 40-60 ºC) as eluent.

1-Piperidino-4-(2´-thienyl)-phthalazine **5a** (example).

This compound was obtained in a 84% yield as a beige solid, mp 125.3-126.3 ºC; ^{1}H NMR ($CDCl_3$) □ 1.70-1.80 (m, 2H, CH_2), 1.80-2.00 (m, 4H, 2xCH_2), 3.40-3.60 (m, 4H, 2xNCH_2), 7.20-7.24 (m, 1H, 4´-H), 7.52 (dd, 1H, 5´-H, J = 4.9, 1.2 Hz), 7.60 (1H, dd, 3´-H, J = 3.2, 1.2 Hz), 7.78-7.80 (m, 2H, 6 and 7-H), 8.08-8.14 (m, 1H, 5 or 8-H), 8.38-8.44 (m, 1H, 8 or 5-H); ^{13}C NMR ($CDCl_3$) □ 24.7, 26.0, 53.4, 121.8, 125.0, 125.9, 126.6, 127.3, 127.7, 128.2, 130.9, 131.5, 139.7, 149.7, 159.9; IR (Nujol) □ 1571, 1489, 1438, 1403, 1306, 1288, 1256, 1215, 1150, 1135, 1114, 1041, 1031, 1111, 931, 913, 874, 846, 892, 848, 695 cm^{-1}; MS: *m/z* (%) = 295 (M^+, 53), 294 (20), 266 (38), 252 (7), 239 (21), 227 (8), 213 (40), 196 (10), 171 (16), 129 (6), 110 (16), 103 (15), 84 (100); HRMS: *m/z* calc. for $C_{17}H_{17}N_3S$: 295.1144; found 295.1144.

Anal. Calcd for $C_{17}H_{17}N_3S$: C, 69.14; H, 5.76; N, 14.23; S, 10.87. Found: C, 68.90; H, 5.94; N, 13.94; S, 10.92.

Acknowledgements

Thanks are due to Foundation for Science and Technology (Portugal) for financial support through IBQF (UM) and through FEDER, POCTI (ref. POCTI/QUI/37816/2001).

References

[1] W. J. Coates, in Comprehensive Heterocyclic Chemistry II, Vol. **6**, A. R. Katritky, C. W. Rees and E. F. V. Scriven, eds, Pergamond Press, Oxford, 1999, 1.

[2] A. E. A. Porter, in Comprehensive Organic Chemistry,Vol. **4**, A. R. Katritky, D. Barton and W. D. Ollis, eds, Pergamond Press, Oxford, 1979; 85.

[3] E. Schaumann and C. Zellerfed, eds, Hetarenes IV, Vol. **E9a**, Houben-Weyl, Germany, 1997; 744.

[4] T. L. Gilchrist, Heterocyclic Chemistry, 3rd ed, Longmans, Oxford, 1997.

[5] M. Napoletano, G. Norcini, F. Pellacini, F. Marchini, G. Morazzoni, P. Ferlenga and L. Pradella, *Bioorg. Med. Chem. Lett.*, **10**, 2235, (2000).

[6] M. Napoletano, G. Norcini, F. Pellacini, F. Marchini, G. Morazzoni, P. Ferlenga and L. Pradella, *Bioorg. Med. Chem. Lett.*, **11**, 33, (2001).

[7] M. Napoletano, G. Norcini, F. Pellacini, F. Marchini, G. Morazzoni, R. Fattori, P. Ferlenga and L. Pradella, *Bioorg. Med. Chem. Lett.*, **12**, 5, (2002).

[8] M. Van der Mey, H. Boss, A. Hatzelmann, I. J. Van der Laan, G. J. Sterk, and H. Timmerman, *J. Med. Chem.*, **45**, 2520, (2002).

[9] G. Bold, *J. Med. Chem.*, **43**, 2310, (2000).

[10] P. G. Tsoungas, M. Searcey, *Tetrahedron Lett.*, **42**, 6589, (2001).

[11] M. Rodríguez-Ciria, A. M. Sanz, M. J. R. Yunta, F. Gomez-Contreras, P. Navarro, I. Fernandez, M. Pardo and C. Cano, C. *Bioorg. Med. Chem.*,**11**, 2143, (2003).

[12] P. Meresse, E. Bertounesque, T. Imbert, C. Monneret, *Tetrahedron*, **55**, 12805, (1999).

[13] T. Hiroyuki, T. Zenji, U. Keiji, A. Yoshio, K. Koji and Y. Hideya,

[19] R. Sivakumar, S. K. Gnanasam, S. Ramachandran and J. T. Leonard, *Eur. J. Med. Chem.*, **37**, 793, (2002).

[20] R. D. Haworth and S. Robinson, *J. Chem. Soc.*, 777, (1948).

[21] F. Kazushi, M. Shinobu and K. Hajime, *Chem. Abstr.*, **130**, 95558c, (1999).

[22] H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.*, **94**, 2483, (1994).

[23] E. Balogh-Hergovich, J. Kaizer and G. Speier, *Inorg. Chim. Acta*, **256**, 9, (1997).

[24] A. Krief and C. Colaux-Castillo, *Tetrahedron Lett.*, **40**, 4189, (1999).

[25] A. Yatani, M. Fuji, Y. Nakao, S. Kashino, M. Kinoshita, W. Mori and S. Suzuki, *Inorg. Chim. Acta*, **316**, 127, (2001).

[26] J. Kuzelka, B. Spingler and S. J. Lippard, *Inorg. Chim. Acta*, **337**, 212, (2002).

[27] Y. Hideyuki, K. Ureshino, J. Ishida, H. Nohta and M. Yamaguchi, *Dyes Pigments*, **41**, 177, (1999).

[28] K. M. Shubin, V. A. Kuznestsov and V. A. Galishev, *Tetrahedron Lett.*, **45**, 1407, (2004).

[29] J. Ishilda M. Yamaguchi, T. Nakahara and M. Nakamura, *Anal. Chim. Acta,* **231**, 1, (1990).

[30] J. Ishilda, S. Sonezaki and M. J. Yamaguchi, *Chromatogr.*, **598**, 203, (1992).

[31] J. Ishilda, T. Yakabe, H. Nohta and M. J. Yamaguchi, *Chromatogr.*, **346**, 175, (1997).

[32] Y. Cheng, B. Ma and F. Wuld, *J. Mat. Chem.*, **9**, 2183, (1999).

[33] S. Guery, I. Parrot, Y. Rival and C.-G. Wermuth, *Synthesis*, 699, (2001).

[34] P. Tapolcsányi, B. U. W. Maes, K. Monsieurs, G. L. F. Lemière, Z. Rield, G. Hajós, , B. V-d. Driessche, R. A. Dommisse and P. Mátyus, *Tetrahedron*, **59**, 5919, (2003).

[35] L. Strekowski, M. Mokrosz and D. B. Marden, PCT Int. Appl. (WO) 89 07,599 (1990); *Chem. Abstr.,* **112**, 77214m, (1990).

[36] Ng. Ph. Buu-Hoï, Ng. Hoan, Ng. D. Xuong, *Recl. Trav. Chim. Pays-Bas,* **69**, 1083, (1950).

[37] I. Parrot, Y. Rival and C. G. Wermuth, *Synthesis*, **7**, 1163, (1999).