A New and Efficient Synthesis of Phthalazin-1(2*H*)-ones

A. M. Bernard,[b] M. T. Cocco,[a]* C. Congiu,[a] V. Onnis,[a] P. P. Piras[b]

[a] Dipartimento Farmaco Chimico Tecnologico, Università di Cagliari, Via Ospedale 72, I-09124 Cagliari, Italy
Fax +39(70)6758553; E-mail tcocco@vaxcal.unica.it
[h] Dipartimento di Scienze Chimiche, Università di Cagliari, Via Ospedale 72, I-09124 Cagliari, Italy

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Abstract: 2-Amino-2-(aroylhydrazono)ethyl aryl ethers, readily obtained from a wide range of aryloxyacetonitriles, are converted to phthalazin-1(2*H*)-ones derivatives in high yields by heating in PrOH in the presence of *p*-TsOH.

Key words: phthalazin-1(2*H*)-ones, ethyl aryl ethers, cyclocondensation

Phthalazin-1(2*H*)-ones bearing a substituent at C-4 are key intermediates in the synthesis of compounds showing highly interesting pharmacological activities, such as antihypertensive,[1] antihistaminic,[2] antimicrobic activities.[3] In particular, it was found that 4-(hydroxymethyl)phthalazin-1(2*H*)-one derivatives inhibit blood platelet aggregation[4] and are active in the treatment of diabetic complications.[5]

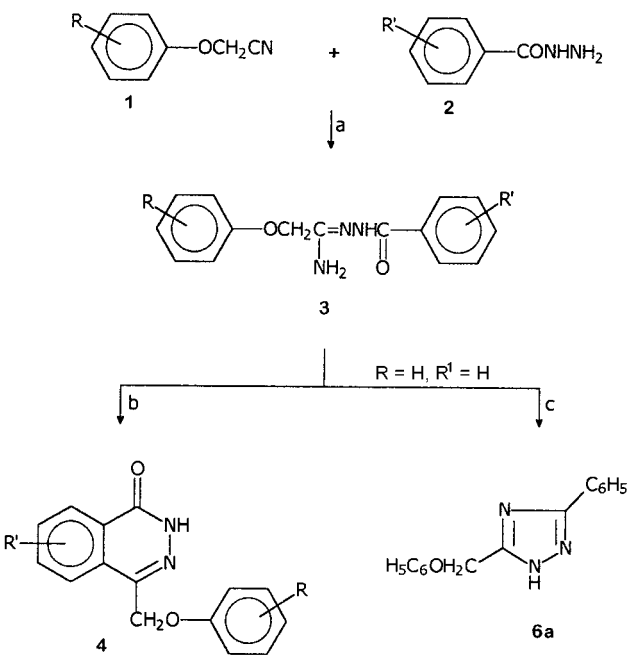
A survey of the available literature reveals that, for the synthesis of these derivatives, 4-(hydroxymethyl)phthalazin-1(2*H*)-one is generally utilized as the starting material. The preparation of this compound proceed via two major multistep pathways with unsatisfactory yields. The first method involves reaction of 2-acetylbenzoic acid with hydrazine,[6] while the second involves reduction of 4-(ethoxycarbonyl)phthalazin-1(2*H*)-ones.[7] In most cases both routes can not be applied for derivatives having substituents on the benzene ring, because of the inaccessibility of the starting compounds.

For these reasons it appears to be interesting to study new and more versatile synthetic methods, that could provide access to a wider variety of substituted phthalazinones.

Our synthetic approach to the phthalazinone derivatives involved the preliminary synthesis of 2-amino-2-(aroylhydrazono)ethyl aryl ethers **3** through the reaction of the corresponding aryloxyacetonitriles **1** and acylhydrazines **2** (Scheme).

The reaction was carried out in ethanol in the presence of sodium ethoxide and gave high yields of derivatives **3** that, as revealed by their ^{1}H NMR spectra, are only present as the amide hydrazone tautomers. The above mentioned **3** were subsequently cyclized to the corresponding phthalazinones **4** by refluxing in PrOH for 6 hours in the presence of a catalytic amount of *p*-TsOH.

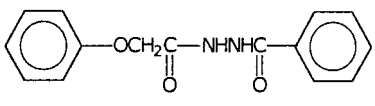
The intramolecular cyclization of 2-amino-2-(aroylhydrazono)ethyl aryl ethers **3** to phthalazinones **4** is likely to involve an electrophilic attack at the *ortho* position of the aroyl ring by the iminic carbon atom. To confirm this hypothesis we reacted 2-amino-2-(aroylhydrazono)ethyl aryl ethers **3** bearing various substituents on the two aromatic rings. Independently from the type and the position of the substituents on the aryloxy aromatic ring high yields of phthalazinones **4** were always obtained. On the contrary, as it is well know that electron-withdrawing substituents decrease the nucleophilicity of the benzene ring, the presence of substituents with -M effect on the aroylhydrazono ring lower the yields or inhibit the reaction completely.



a) NaOEt, EtOH; b) *p*-TsOH, PrOH, reflux; c) $AlCl_3$, toluene, reflux

Scheme

The change from propanol to other polar protic solvents, such as ethanol, decreased reaction rates and yields. The reaction must be carried out in carefully anhydrous conditions as the presence of traces of water gave rise to a drastic decrease in the yields of phthalazinones due to the formation of hydrolysis compounds of **3**. In fact from the reaction of **3a** carried out in aqueous PrOH a mixture of phthalazinone **4a** and 1-benzoyl-2-(phenoxyacetyl)hydrazine **5a** was obtained.



5a

To obtain more information regarding the role of the solvent we tested a variety of experimental conditions on 2-amino-2-(benzoylhydrazono)ethyl phenyl ether **3a**. We found that only the phthalazinone **4a** was obtained by mild heating of a mixture of compound **3a** in $AcOH/H_2SO_4$ in a 5:1 ratio, whereas, carrying out the reaction in an apolar solvent, such as toluene, in the presence of a catalytic amount of $AlCl_3$ gave the triazole derivative **6a** instead. The same compound **6a** was also formed by cyclization of **3a** with $POCl_3$.

It is important to note that, on the basis of compelling spectroscopic evidence, the heterocyclization does not, in

Table 1. 2-Amino-2-(aroylhydrazono)ethyl Aryl Ethers **3** Prepared

Product[a]	R	R′	Yield (%)	mp (°C)[b] (solvent)	IR (Nujol) ν (cm^{-1})	^{1}H-NMR (DMSO-d_6/TMS) δ
3a	H	H	50	190 (EtOH)	3450, 3380, 3160, 1650, 1630	4.51 (s, 2H, CH_2), 6.54 (s, 2H, NH_2), 7.01, 7.29, 7.45, 7.80 (m, 10H_{arom}), 9.87 (s, 1H, NH)
3b	2-CH_3	H	65	170 (EtOH)	3480, 3200, 1670, 1630	2.19 (s, 3H, CH_3), 4.52 (s, 2H, CH_2), 6.51 (s, 2H, NH_2), 6.83, 7.00, 7.43, 7.80 (m, 9H_{arom}), 9.90 (s, 1H, NH)
3c	3-CH_3	H	80	168 (EtOH)	3450, 3190 1660, 1600,	2.25 (s, 3H, CH_3), 4.48 (s, 2H, CH_2), 6.52 (s, 2H, NH_2), 6.80, 7.15, 7.44, 7.79 (m, 9H_{aromm}), 9.86 (s, 1H, NH)
3d	4-CH_3	H	77	170 (EtOH)	3470, 3140 1670, 1625, 1605, 1575	2.20 (s, 3H, CH_3), 4.48 (s, 2H, CH_2), 6.59 (s, 2H, NH_2), 6.91, 7.07, 7.43, 7.81 (m, 9H_{arom}), 9.90 (s, 1H, NH)
3e	2-OCH_3	H	55	190 (MeOH)	3400, 3210, 1670, 1630, 1610, 1590	3.75 (s, 3H, CH_3), 4.50 (s, 2H, CH_2), 6.54 (s, 2H, NH_2), 6.87, 6.95, 7.08, 7.43, 7.81 (m, 9H_{arom}), 9.90 (s, 1H, NH)
3f	3-OCH_3	H	87	180 (EtOH)	3420, 3220, 1675, 1645, 1600	3.68 (s, 3H, CH_3), 4.49 (s, 2H, CH_2), 6.57 (s, 2H, NH_2), 6.51, 7.14, 7.41, 7.78 (m, 9H_{arom}), 9.92 (s, 1H, NH)
3g	4-OCH_3	H	65	190 (EtOH)	3460, 3150, 1675, 1640, 1610, 1580	3.66 (s, 3H, CH_3), 4.45 (s, 2H, CH_2), 6.52 (s, 2H, NH_2), 6.92, 7.43, 7.79 (m, 9H_{arom}), 9.86 (s, 1H, NH)
3h	2-Cl	H	73	187 (EtOH)	3420, 3190, 1675, 1640, 1620, 1600	4.58 (s, 2H, CH_2), 6.54 (s, 2H, NH_2), 6.94, 7.24, 7.41, 7.78 (m, 9H_{arom}), 9.93 (s, 1H, NH)
3i	3-Cl	H	85	190 (EtOH)	3430, 3200, 1680, 1650, 1630, 1600	4.52 (s, 2H, CH_2), 6.55 (s, 2H, NH_2), 6.98, 7.07, 7.29, 7.43, 7.77 (m, 9H_{arom}), 9.87 (s, 1H, NH)
3j	4-Cl	H	80	197 (EtOH)	3440, 3190, 1680, 1640, 1625, 1595	4.53 (s, 2H, CH_2), 6.60 (s, 2H, NH_2), 7.04, 7.32, 7.44, 7.80 (m, 9H_{arom}), 9.89 (s, 1H, NH)
3k	4-NO_2	H	92	148 (PrOH)	3440, 3350, 3170, 1620, 1585	4.70 (s, 2H, CH_2), 6.55 (s, 2H, NH_2), 7.21, 7.34, 7.87, 8.18 (m, 9H_{arom} + NH)
3l	H	2-CH_3	78	185 (PrOH)	3440, 3230, 1690, 1650, 1630, 1600	2.28 (s, 3H, CH_3), 4.46 (s, 2H, CH_2), 6.40 (s, 2H, NH_2), 6.82–7.32 (m, 9H_{arom}), 9.81 (s, 1H, NH)
3m	H	3-CH_3	70	150 (EtOH)	3460, 3210, 1690, 1655, 1630	2.31 (s, 3H, CH_3), 4.49 (s, 2H, CH_2), 6.53 (s, 2H, NH_2), 6.94, 7.00, 7.27, 7.60 (m, 9H_{arom}), 9.83 (s, 1H, NH)
3n	H	4-CH_3	76	190 (PrOH)	3460, 3430, 3220, 1675, 1630	2.30 (s, 3H, CH_3), 4.49 (s, 2H, CH_2), 6.54 (s, 2H, NH_2), 6.92, 6.99, 7.27, 7.70 (m, 9H_{arom}), 9.82 (s, 1H, NH)
3o	H	2-Cl	78	195 (PrOH)	3420, 3210, 1680, 1640, 1615, 1590	4.47 (s, 2H, CH_2), 6.41 (s, 2H, NH_2), 6.83–7.48 (m, 9H_{arom}), 9.96 (s, 1H, NH)
3p	H	3-Cl	84	150 (EtOH)	3430, 3220, 1680, 1640, 1620, 1600	4.51 (s, 2H, CH_2), 6.62 (s, 2H, NH_2), 6.93, 6.99, 7.26, 7.43, 7.80 (m, 9H_{arom}), 10.00 (s, 1H, NH)
3q	H	4-Cl	58	180 (PrOH)	3440, 3370, 3230, 1680 1645, 1620	4.50 (s, 2H, CH_2), 6.58 (s, 2H, NH_2), 6.98, 7.27, 7.47, 7.83 (m, 9H_{arom}), 9.94 (s, 1H, NH)

[a] Satisfactory microanalyses obtained for all compounds.
[b] Uncorrected melting points.

any case, proceed to give benzofuran derivatives which could also be obtained from compounds **3** in acidic medium.

Melting points were determined on a Kofler hot stage and are uncorrected. IR spectra were recorded on Nujol mulls between NaC1 plates on a Perkin–Elmer 398 spectrophometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity 300 spectrometer. MS were recorded with a Fisons QMD 1000 spectrometer in EI mode at 70 eV. Elemental analyses were carried out with a Carlo Erba Model 1106 Elemental Analyzer.

2-Amino-2-(aroylhydrazono)ethyl Aryl Ethers 3; General Procedure:
To a stirred solution of NaOEt (0.005 mol) in anhyd EtOH (5 mL) was added the appropriate aryloxyacetonitrile **1** (0.05 mol). The mixture was stirred at r.t. for 1 h and, after cooling to 0 °C, an ethanolic solution of aroylhydrazine **2** (0.05 mol) was added dropwise. The resulting solution was stirred at the same temperature for 2 h and then allowed to reach r.t. and stand ovemight. The formed precipitate was collected by filtration and recrystallized from the solvent given in Table 1.

4-(Phenoxymethyl)phthalazin-2(1*H*)-one (4a); Typical Procedure:
Method A: To a suspension of 2-amino-2-(benzoylhydrazono)ethyl phenyl ether (**3a**; 0.5 g, 1.85 mmol) in anhyd PrOH (15 mL) was added *p*-TsOH (0.15 g, 0.9 mmol). After heating at reflux for 6 h the solvent was removed in vacuo and the residue treated with H_2O (20 mL) and extracted with $CHCl_3$ (3 × 10 mL). The organic layers were dried (Na_2SO_4) and the solvent evaporated to give the crude **4a** which was **p**urified by recrystallization (hexane); yield: 0.4 g (86%).
^{13}C NMR ($CDCl_3$): δ = 59.67 (t, CH_2), 114.60 (d, C-2′, C-6′), 121.95 (d, C-4′), 123.21 (s, C-10), 126.83 (d, C-5, C-8), 128.83 (d, C-3′, C-5′), 129.49 (d, C-7), 129.86 (s, C-9), 131.79 (d, C-6, C-7), 157.31 (s, C-4), 162.09 (s, C-1′), 166.55 (s, C-1)
MS: *m/z* (%) = 252 (M^+, 45), 159 (87), 105 (100), 77 (41)

Method B: To 2-amino-2-(benzoylhydrazono)ethyl phenyl ether (**3a**; 0.5 g, 1.85 mmol) in AcOH (5 mL) was added 96% H_2SO_4 (3 drops) and the resulting solution was stirred at r.t. for 0.5 h. The precipitated phthalazinone **4a** was filtered off, washed with H_2O and purified as described above; yield: 0.46 g (98%).

1-Benzoyl-2-(phenoxyacetyl)hydrazine (5a):
To a suspension of 2-amino-2-(benzoylhydrazono)ethyl phenyl ether (**3a**; 0.5 g, 1.85 mmol) in aq PrOH (15 mL) was added *p*-TsOH

Table 2. 4-(Aryloxymethyl)phthalazin-2(1*H*)-one Derivatives **4** Prepared

Product[a]	R	R′	Yield (%)	mp (°C)[b] (Solvent)	IR (Nujol) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ
4a	H	H	86	95 (hexane)	3060, 1600	5.28 (s, 2H, CH_2), 6.98, 7.01, 7.48, 8.02 (m, 9H+ NH)
4b	2-CH_3	H	93	87 (cyclohexane)	3060, 1600	2.27 (s, 3H, CH_3),5.34 (s, 2H, CH_2), 6.97, 7.17, 7.54, 8.08 (m, 8H$_{arom}$ + NH)
4c	3-CH_3	H	94	71 (hexane)	3040, 1610	2.28 (s, 3H, CH_3), 5.25 (s, 2H, CH_2), 6.80, 7.17, 7.43, 8.03 (m, 8H$_{arom}$ + NH)
4d	4-CH_3	H	98	80 (cyclohexane)	3050, 1610, 1585	2.30 (s, 3H, CH_3), 5.30 (s, 2H, CH_2), 6.95, 7.12, 7.50, 8.08 (m, 8H$_{arom}$ + NH)
4e	2-OCH_3	H	89	85 (hexane)	3080, 1600	3.80 (s, 3H, CH_3), 5.31 (s, 2H, CH_2), 6.94, 7.43, 8.01 (m, 8H$_{arom}$ + NH)
4f	3-OCH_3	H	97	90 (cyclohexane)	3060, 1605, 1595	3.80 (s, 3H, CH_3), 5.32 (s, 2H, CH_2), 6.61, 7.22, 7.53, 8.08 (m, 8H$_{arom}$ + NH)
4g	4-OCH_3	H	98	85 (cyclohexane)	3040, 1610	3.77 (s, 3H, CH_3), 5.27 (s, 2H, CH_2), 6.86, 6.98, 7.53, 8.08 (m, 8H$_{arom}$ + NH)
4h	2-Cl	H	65	125 (cyclohexane)	3060, 1590	5.40 (s, 2H, CH_2), 6.97, 7.18, 7.41, 7.53, 8.08 (m, 8H$_{arom}$ + NH)
4i	3-Cl	H	92	95 (cyclohexane)	3060, 1595, 1580	5.32 (s, 2H, CH_2), 7.00, 7.22, 7.53, 8.08 (m, 8H$_{arom}$ + NH)
4j	4-Cl	H	98	124 (ligroine)	3060, 1600	5.47 (s, 2H, CH_2), 7.13, 7.34, 7.59, 7.97 (m, 8H$_{arom}$ + NH)
4k	4-NO_2	H	63	156 (benzene)	3060, 1585	5.37 (s, 2H, CH_2), 7.10, 7.46, 8.01, 8.19 (m, 8H$_{arom}$ + NH)
4l	H	6-CH_3	30	140 (*i*-PrOH)	3050, 1625, 1600	2.36 (s, 3H, CH_3), 5.25 (s, 2H, CH_2), 7.00, 7.26, 7.87 (m, 8H$_{arom}$ + NH)
4m	H	7-CH_3	97	68 (hexane)	1600, 1550, 1500	1.61 (s, 3H, CH_3), 5.33 (s, 2H, CH_2), 7.06, 7.35, 7.90 (m, 8H$_{arom}$ + NH)
4n	H	8-CH_3	98	75 (hexane)	3040, 1600, 1585, 1540	2.70 (s, 3H, CH_3), 5.35 (s, 2H, CH_2), 7.05, 7.31, 7.43, 7.95 (m, 8H$_{arom}$ + NH)
4o	H	6-Cl	43	70 (hexane)	3050, 1600, 1580	5.26 (s, 2H, CH_2), 6.99, 7.26, 7.43, 7.95 (m, 8H$_{arom}$ + NH)
4p	H	7-Cl	87	60 (hexane)	3050, 1580	5.26 (s, 2H, CH_2), 6.99, 7.38, 7.45, 7.92, 8.00 (m, 8H$_{arom}$ + NH)
4q	H	8-Cl	83	75 (hexane)	300, 1590, 1580	5.27 (s, 2H, CH_2), 7.06, 7.30–7.57, 8.00 (m, 8H$_{arom}$ + NH)

[a] Satisfactory microanalyses obtained for all compounds.
[b] Uncorrected melting points.

(0.15 g, 0.9 mmol). After heating at reflux for 6 h, the formed precipitate was filtered off and recrystallized from *i*-PrOH to give **5a**; yield: 0.25 g (50%); mp 185 °C.
IR (Nujol): ν = 3420, 3220, 1700, 1660 cm^{-1}.
^1H NMR (DMSO-d_6): δ = 4.60 (s, 2H, CH_2), 6.97, 7.26, 7.46, 7.83 (m, 10H_{arom}), 10.29 (br s, 2H, NH).
From evaporation of the mother solution phthalazinone **4a** was isolated in 20% yield.

5-(Phenoxymethyl)-3-phenyl-(1*H*)-1,2,4-triazole (6a):
Method A: A mixture of 2-amino-2-(benzoylhydrazono)ethyl phenyl ether (**3a**; 0.5 g, 1.85 mmol) and $AlCl_3$ (0.25 g, 1.85 mmol) in anhyd toluene (50 mL) was heated at reflux for 10 h. The solvent was evaporated to give the triazole **6a** (0.36 g, 85%) which was recrystallized (benzene); mp 157 °C.
IR (Nujol): ν = 3130, 3030, 1590, 1580 cm^{-1}.
^1H NMR (DMSO-d_6): δ = 5.16 (s, 2H, CH_2), 6.90, 7.23, 7.33, 7.94 (m, 11H, Ar + NH).

Method B: A mixture of 2-amino-2-(benzoylhydrazono)ethyl phenyl ether (**3a**; 0.5 g, 1.85 mmol) and $POCl_3$ (5 mL) was heated at reflux for 3 h. After cooling, H_2O was added and the formed precipitate filtered off and worked up as in Method A to give the triazole derivative in 66% yield.

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