Indian Journal of Chemistry
Vol.36B, July 1997, pp.612 - 616

Note

Utility of arylhydrazidoyl aryl ethers in heterocycles : A novel synthesis of aryloxy-pyridazines, phthalazines and thieno-[3,4-*d*]pyridazine derivatives

M K A Ibrahim*, A H H Elghandour & B El-Badry

Department of Chemistry, Faculty of Science, Cairo University, Giza, Egypt

Received 30 November 1995; revised and accepted 18 November 1996

The reaction of hydrazidoyl chloride **1** with *p*-bromophenol afford the ether derivative **2** which on treatment with ethyl cyanoacetate furnish 6-(4-bromophenyloxy)-4-cyano-2, 3-dihydro-5-methyl-2-phenyl-3-pyridazinone **3**. Compound **3** is then utilized to synthesize a variety of heterocyclic compounds such as phthalazine derivatives, **6a-c, 10a,b, 12** and **14**. Also, it is utilized in the synthesis of thieno[2,3-*d*]pyridazine derivative **15**, which undergoes chemical transformations to afford several new heterocyclic compounds. All structures have been established on the basis of elemental analyses and spectral data.

In continuation of our interest in the chemistry of hydrazidoyl halides[1-4] and synthesis of arylhydrazinoyl aryl ethers and their thermal rearrangement[5], an attempt was made to utilize arylhydrazidoyl aryl ethers in the synthesis of heterocycles.

Thus, hydrazidoyl chloride **1** was reacted with *p*-bromophenol in the presence of sodium ethoxide to afford the aryl ether derivative **2** which on treatment with ethyl cyanoacetate in the presence of ammonium acetate afforded the pyridazine derivative **3**[6-8]. Its structure was established on the basis of elemental analysis and spectral data. Its IR spectrum revealed an absorption band at 2220 cm^{-1} for the cyano group, while the ^1H NMR spectrum revealed a singlet at δ2.7 ppm for the methyl protons and a multiplet at δ7.1-76 for the aromatic protons. Compound **3**, in turn, on treatment with arylidene malononitriles **4a-c** yielded phthalazine derivatives **6a-c**, respectively. The formation of **6a-c** is assumed to proceed via Michael addition to afford the non-isolable intermediate **5**, which underwent cyclization followed by spontaneous aromatization, via loss of hydrogen cyanide, to yield **6a-c**. Compound **6a** was also prepared by treatment of **3** with benzaldehyde to afford the benzylidene derivative **7** followed by treatment with malononitrile. Similarly, compound **3** was treated with substituted α-benzoyl cinnamonitriles **9a-b**, ethyl α-cyanocinnamate **11** and furfurylidene malononitrile **13** to afford the corresponding phthalazine derivative **10a,b, 12** and **14** respectively (Scheme I). Structures of **10a,b, 12** and **14** were established on the basis of elemental analyses and spectral data (cf. Table I).

Compound **3** on reaction with elemental sulfur in the presence of triethylamine furnished thieno[3,4-*d*]pyridazine derivative **15**. Its structure was confirmed on the basis elemental analysis and spectral data. Its IR spectrum revealed absorption bands in the range 3400-3200 cm^{-1} due to the amino group and the absence of any absorption in the range 2500-2100 cm^{-1} was due to the cyano group. ^1H NMR spectrum showed signals at δ6.3 for the amino group, at 6.5 for the thieno proton and at 7.3-7.7 due to the aromatic protons. Compound **15** also underwent acetylation and benzoylation to afford the corresponding N-acyl derivatives **16** and **17**, respectively. Bromination of **15** in chloroform afforded the bromo derivative **18**. Structures of **16-18** were established on the basis of elemental analyses and spectral data.

Compound **15** on reaction with phenyl and acetyl isothiocyanates furnished the corresponding thiocarbamoyl derivatives **19** and **20** respectively, rather than the corresponding thiourea derivatives. The formation of the thiocarbamoyl derivatives were established on the basis of their ^1H NMR spectra, which revealed the absence of any signals due to the thieno proton (cf. Scheme II and Table I).

Compound **15** on reaction with acrylonitrile gave the phthalazine derivative **22**. The formation of **22** is assumed to proceed via cycloaddition of acrylonitrile to compound **15** to afford the non-isolable intermediate **21** which is aromatized via loss of hydrogen sulfide. Compound **15** also reacted with maleic anhydride and *N*-phenylmaleimide to afford the corresponding furo[3,4-*f*]-phthalazine and pyrrolo[3,4-*f*]phthalazine derivatives **24a,b** respectively. The formation of **24a,b** is assumed to proceed via dipolar cycloaddition to give intermediates **23a,b** which is converted to **24a,b** via loss of hydrogen sulfide. All structures

Table I—Characterization data for the newly synthesized compounds

Compd*	m.p. (°C)	Yield (%)	Mol. formula (Mol wt)	^{1}H NMR δ, ppm)
1	80	80	$C_{15}H_{13}BrN_2O_2$ (333.190)	—
3	235	83	$C_{18}H_{12}BrN_3O_2$ (382.222)	2.7 (s, 3H, CH_3); 7.1-7.6 (m, 9H, Ar-H)
6a	255	75	$C_{27}H_{17}BrN_4O_2$ (509.368)	—
7a	215	75	$C_{25}H_{16}BrN_3O_2$ (470.331)	7.0-8.0(m, 15H, Ar-H), 8.5(s, 2H, NH_2)
10a	215	75	$C_{33}H_{22}BrN_3O_3$ (588.466)	—
10b	>300	73	$C_{34}H_{24}BrN_3O_4$ (618.492)	3.4(s, 3H, CH_3O), 7.0-8.3(m, 19H), 9.0 (s, 2H, NH_2).
12	158	70	$C_{29}H_{22}BrN_3O_4$ (556.421)	0.8(t, 3H, CH_3), 4.0(q, 2H, CH_2), 7.1-7.7(m, 15H, Ar-H), 8.3(s, br, 2H, NH_2).
14	>300	63	$C_{25}H_{15}BrN_4O_3$ (499.329)	—
15	190	75	$C_{18}H_{12}BrN_3O_2S$ (414.286)	6.2(s, 2H, NH_2), 6.5(s, 1H, thieno proton), 7.2-7.7(m, 9H, Ar-H)
16	202	65	$C_{20}H_{14}BrN_3O_3S$ (456.323)	6.2(s, 2H, CH_3), 6.4(s, 1H, thieno proton), 6.8-7.9(m, 10H, Ar-H), 8.9(s, 1H, NH)
17	225	78	$C_{25}H_{16}BrN_3O_3S$ (518.394)	6.4(s, 1H, thieno proton), 7.0-7.9(m, 14H, Ar-H), 8.3(s, br, 1H, NH).
18	210	72	$C_{18}H_{11}Br_2N_3O_2S$ (493.187)	6.9-7,9(m, 9H, Ar-H), 11.0(s, 2H, NH_2).
19	260	65	$C_{25}H_{17}BrN_4O_2S_2$ (549.474)	6.8-7.4(m, 14H, Ar-H), 10.2(s, br, 1H, NH), 11.5(s, br, 2H, NH_2)
20	240	60	$C_{21}H_{15}BrN_4O_3S_2$ (515.413)	2.9(s, 3H, CH_3); 6.8-8.0(m, 9H, Ar-H), 9.2(s, br, 1H, NH), 11.2(s, br, 2H, NH_2)
22	216	70	$C_{21}H_{13}BrN_4O_2$ (433.270)	—
24a	250	70	$C_{22}H_{12}BrN_3O_5$ (478.263)	—
24b	175	60	$C_{28}H_{17}BrN_4O_4$ (553.377)	—

*Satisfactory C, H, N and S analyses were obtained for the compounds. Compounds were routinely checked from their IR data.

were confirmed on the basis of elemental analyses and spectral data (cf. Scheme II and Table I).

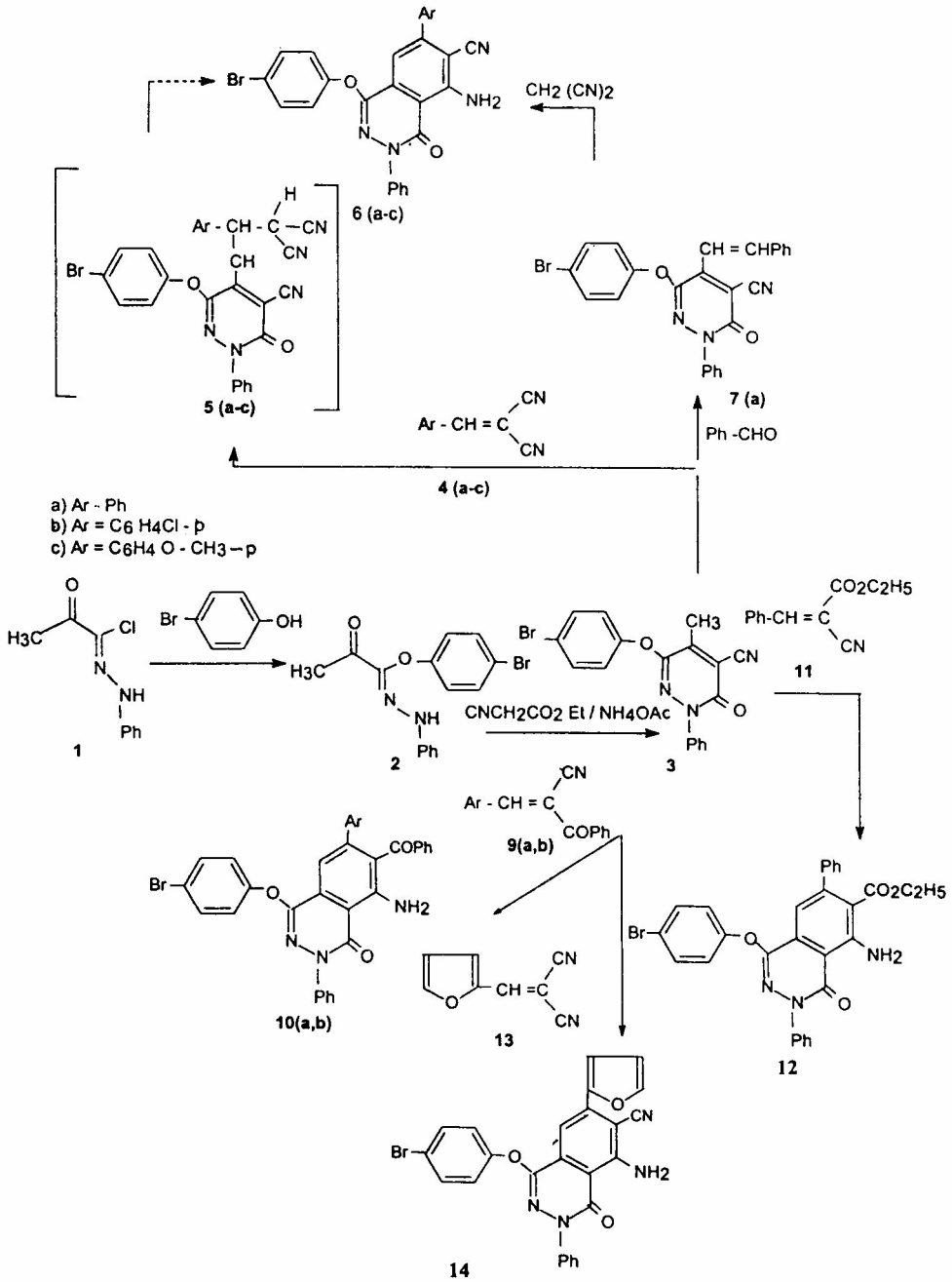
Experimental Section

M.ps were determined on a Gallenkamp melting point apparatus. IR spectra were recorded in KBr using a Shimadzu spectra 200-91506 spectrophotometer, ^{1}H NMR spectra in DMSO on a Varian 90 MHz using TMS as the internal reference. Elemental analyses were carried out by the Microanalytical Center at Cairo University. All physical and elemental data of the products are listed in Table I.

Reaction of 1 with *p*-bromophenol: Synthesis of 2. Compound **1** (0.01 mole) was added to a solution of *p*-bromophenol (0.01 mole) in abs. ethanol (20 mL) containing sodium (0.01 mole). The reaction mixture was stirred for 3 hr at room temp. and left overnight. It was then poured over crushed ice and neutralized with HCl. The solid formed was collected by filtration, washed with water and crystallized from ethanol to afford **2**.

6-(*p*-Bromophenyloxy)- 4- cyano-2, 3-dihydro-5-methyl-2-phenyl-pyridazine-3-one 3. A mixture **2** (0.01 mole), ethyl cyanoacetate (0.01 mole) and ammonium acetate (0.02 mole) was heated for 1 hr at 120°C. The reaction mixture was then poured over crushed ice and the solid obtained was collected by filtration and crystallized from ethanol to afford **3**.

6-(*p*-Bromophenyloxy)- 4- cyano-2, 3-dihydro-5-styryl-2-phenyl-pyridazine-3-one 7. The appropriate aromatic aldehyde (0.01 mole) was added to a solution of **3** (0.01 mole) in ethanol (20 mL), containing piperidine (0.5 mL). The reaction mixture was refluxed for 3 hr, cooled and poured



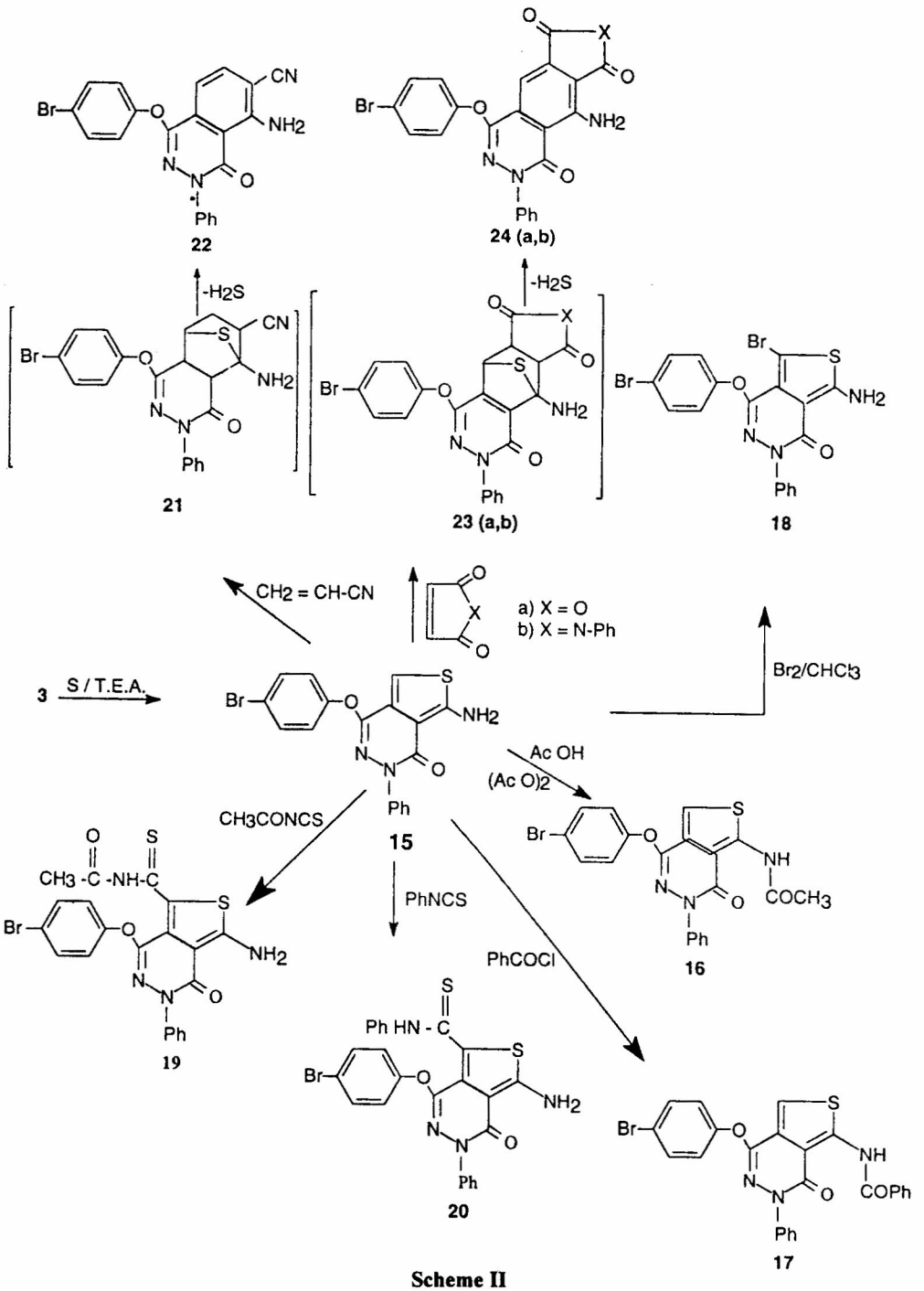
Scheme I

over ice/HCl mixture. The solid formed was collected by filtration, washed with water and crystallized from dioxane-ethanol to afforded **7**.

4-Amino- 8- (*p*-bromophenyloxy)-5-cyano-2, 3-dihydro- 6- aryl- 2- phenyl-phthalazine- 3- one 6: Method A. To a solution of **7** (0.01 mole) in ethanol (20 mL) containing piperidine (0.5 mL), was added malononitrile (0.01 mole). The reaction mixture was refluxed for 3 hr, cooled and poured over ice/HCl mixture. The product was collected by filtration, washed with water and crystallized from ethanol-DMF to afford **6**.

Method B. A mixture of **3** (0.01 mole) and the appropriate α-cyanocinnamonitrile derivative, **6a-c** (0.01 mole) in ethanol (25 mL), containing piperidine (0.5 mL) was refluxed for 3 hr. The reaction mixture was then cooled and poured over ice-HCl mixture. The solid formed was collected by filtration, washed with water and crystallized from ethanol-DMF to afford products, identical in all aspects (elemental analyses, m.p. and spectral data) to those obtained from Method A.

Synthesis of the phthalazine derivatives 10a,b, 12 and 14. A mixture of **3** (0.01 mole) and each



Scheme II

of α-benzoyl cinnamonitrile derivatives **9a,b**, ethyl α-cyanocinnamate **11** or furfurylidene malononitrile **13** (0.01 mole) in ethanol (25 mL), containing piperidine (0.5 mL) was refluxed for 3 hr. The reaction mixture was then cooled and poured over ice-HCl mixture. The solid formed was collected by filtration, washed with water and crystallized from ethanol-DMF to afford compounds **10a,b, 12** and **14** respectively.

Synthesis of the thienoprydazine derivative 15. Compound **3** (0.01 mole) was added to a suspension of sulfur (0.01 mole) in ethanol (30 mL), containing triethyl amine (0.01 mole). The reaction mixture was refluxed for 3 hr, cooled and poured over ice-HCl mixture. The solid formed was collected by filteration, washed with water and crystallized from dioxane-ethanol to afford **15**.

Acylation and benzoylation of 15. Compound **15** (0.01 mole) was added to a mixture of acetic anhydride (10 mL) and acetic acid (20 mL). The reaction mixture was refluxed for 3 hr, cooled and poured over ice. The solid formed was collected by filtration, washed with water and crystallized from dioxane-ethanol to afford **16**.

Compound **15** (0.01 mole) was added to solution of benzoyl chloride (0.01 mole) in pyridine (30 mL). The reaction mixture was refluxed for 3 hr, cooled and poured over ice-HCl mixture. The solid product was collected by filtration, washed with water and crystallized from dioxane-ethanol to afford **17**.

Bromination of 15. To a solution of **15** (0.01 mole) in chloroform (30 mL) was added bromine (0.01 mole) in chloroform (10 mL). The reaction mixture was stirred at room temperature for 2 hr and the chloroform was then evaporated. The solid product obtained was triturated with ethanol and crystallized from dioxane-ethanol to afford **18**.

Synthesis of 19 and 20. Compound **15** (0.01 mole) was added to a solution of phenyl isothiocyanate (0.01 mole) and acetyl isothiocyanate in dry pyridine. The reaction mixture was refluxed for 3 hr, cooled and poured over ice-HCl mixture. The solid product formed was collected by filtration, washed with water and crystallized from ethanol-DMF to afford compounds **19** and **20** respectively.

Reaction of 15 with dienophiles. Compound **15** (0.01 mole) was added to a solution of 0.01 mole of each of acrylonitrile, maleic anhydride or *N*-phenylmaleimide in pyridine (20 mL). The reaction mixture was refluxed for 5 hr, cooled and poured over ice-HCl mixture. The solids formed were collected by filtration, washed with water and crystallized from ethanol-DMF to afford compounds **22** and **24a,b** respectively.

References

1 Elnagdi M H, Elmoghayer M R H, Kandeel E M & Ibrahim M K A, *J Heterocyl Chem*, 14, **1977**, 227.

2 Elmoghayer M R H, Elnagdi M H, Ibrahim M K A & Sallam M M M, *Helv Chim Acta*, 60, **1977**, 2171.

3 Ibrahim M K A, El-gharib M S, Farag A M & Elghandour A H H, *Indian J Chem*, 27B, **1988**, 836.

4 Ibrahim M K A, *Phosph, Sulfur & Silicon*, 47, **1990**, 61.

5 Shawali A S & Ibrahim M K A, *Bull Chem Soc Jpn*, **1973**, 3625.

6 Elnagdi M H, Ibrahim N S, Sadek K U & Mohamed M H, *Liebg's Ann Chem*, **1988**, 1005.

7 Elnagdi M H, Negm A M & Eriam A W, *Liebg's Ann Chem*, **1989**, 1255.

8 Elnagdi M H, Abdelrazek F M, Ibrahim N S & Erian A W, *Tetrahedron*, 45, **1989**, 3597.