Synthesis of new phthalazinedione derivatives

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"Abstract." Heterocycles containing phthalazine moiety have been a subject of great interest. They have been reported by their anticonvulsant, cardiotonic and vasorelaxant activities. Despite the number of available methods for their synthesis, the development of new synthetic methods for the efficient preparation of heterocycles containing phthalazine fragment is an interesting challenge. Therefore, we have synthesized new phthalazine-1,4-dione derivatives by introduction of halogenoalkyl substituents on the NH-nucleophilic groups. The described synthetic route will allow us to condense a nitrogen heterocyclic ring on the phthalazinone moiety and obtain a new tricyclic scaffold with promising pharmacological properties.

Key words: heterocycles, phthalazine, synthesis, pharmacological properties.

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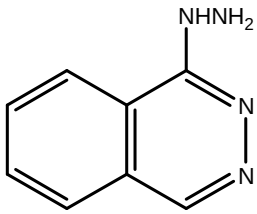
Introduction

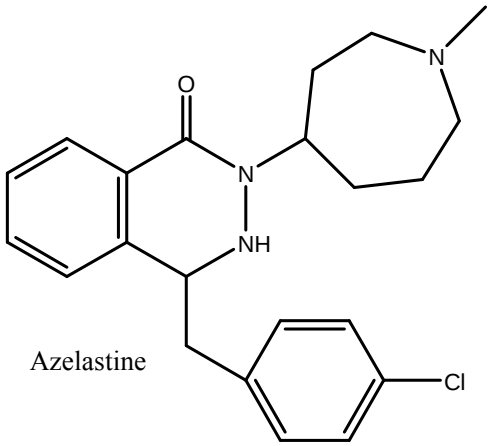
The discovery of the first naturally occurring pyridazine derivative (pyridazomycin) meant a milestone in the recognition of the potential of the 1,2-diazine core as a valuable unit in medicinal chemistry.[1] In particular, 3 oxo derivatives [pyridazin-3(2H)-one scaffold] have shown a wide range of biological actions, specially on targets that play a key role in cardiovascular diseases.[2] Hydralazine is also a hydrazine derivative used clinically as a vasodilator and antihypertensive agent.[3] More recently, several 4-substituted phthalazin-1-one have been reported because they afforded total relaxation on isolated rat aorta rings pre-contracted with phenylephrine at micromolar concentration.[4] Azelastine is a relevant member of this family of compounds which has also demonstrated to induce vasorelaxation *in vitro* assays, more over of other interesting pharmacological activities.[5]

With these precedents and with the aim of preparing new derivatives with potential pharmacological activity, we have synthesized new phthalazinone derivatives in which, 4-substituent of azelastine is replaced by a carbonyl group.[6] Additionally halogenoalkyl substituents with different chain length have been introduced on the NH-nucleophilic groups.[7] Finally, using a nucleophilic reaction the halogen group was substituted by an azide group.[8]

The described derivatives bearing N-alkylazide groups will allow us to condense a nitrogen heterocyclic ring on the phthalazinone moiety obtaining a new tricyclic scaffold with promising pharmacological properties.[9, 10]



Hidralazine



Azelastine

Results and discussion

8-Chloro-2-methyl-2,3-dihydrophthalazine-1,4-dione (**1a**) and 5-chloro-2-methyl-2,3-dihydrophthalazine-1,4-dione (**1b**) were obtained from reaction of 4-chlorophtalic anhydride with methylhydrazine and subsequent separation by HPLC resulting the isomer **1a** as majority compound of the mixture.

Compounds **2b**, **2c** and **2d** were obtained by N- alkylation of the phthalazine-1,4-dione derivatives using dihalogenoalkyl groups with different length chains after removing hydrogen atom of NH group in basic conditions. However, 2-(2-bromo-ethyl)-8-chloro-2-methyl-2,3-dihydrophthalazine-1,4-dione] (**2a**) resulted a very unstable derivative and it was not isolated following the described procedure.

Finally, by nucleophilic substitution of the halogen groups, were obtained the azide derivatives **3a**, **3b** and **3c**.

All the new derivatives were obtained in good yields.

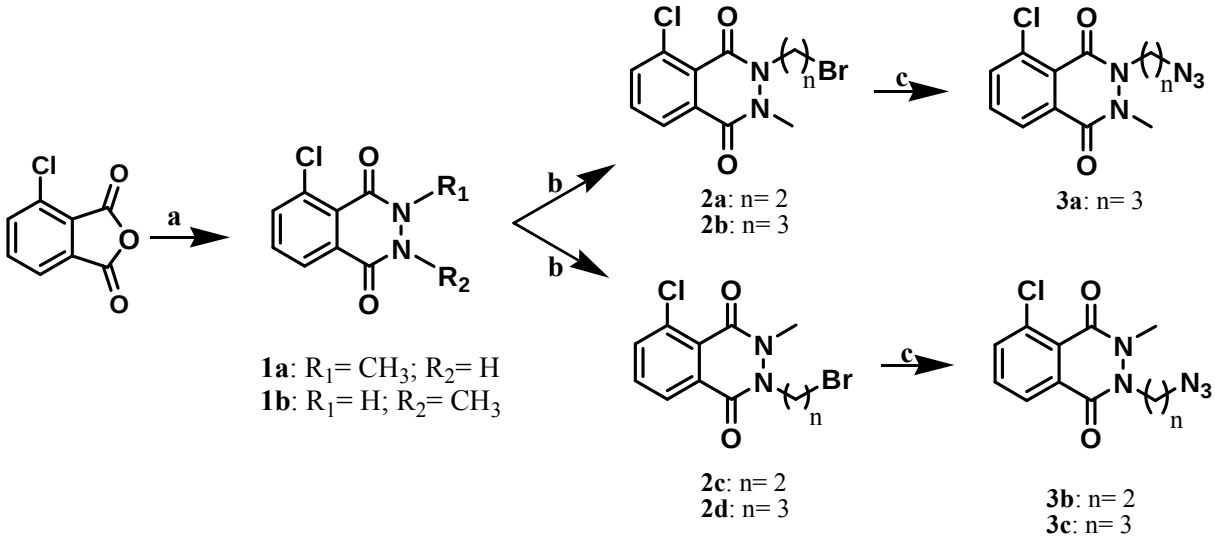
Chemistry

The phthalazine-1,4-dione derivatives were efficiently synthesized according to the synthetic protocol outlined in **Scheme 1**.

Preparation of phthalzine-1,4-diones **1a** and **1b** was performed using microwaves assisted Gabriel synthesis by reaction of 4-chlorophtalic anhydride and methylhydrazine.[6] The resulting compounds were separated by HPLC.

Phthalzine-1,4-diones, **1a** and **1b** reacted with either 1,3-dibromopropane or 1,2-dibromoethane, using K_2CO_3 in acetone affording the compounds **2b**, **2d** and **2c** respectively.[7] However, because of its instability, it was not possible to isolate the compound **2a**.

Finally the reaction of N, N-dialkyl-5-chloro-2,3-dihydro-phthalazine-1,4-dione derivatives **2b**, **2c** and **2d** were done to react with sodium azide and NaI in DMSO to 100ºC affording compounds **3a**, **3b** and **3c** respectively.[8]



Reagents and Conditions: a) CH_3NHNH_2, MW; b) $Br(CH_2)_nBr$, K_2CO_3, $(CH_3)_2CO$, reflux; c) NaN_3, NaI, DMSO, 100 ºC.

Scheme 1

Conclusions

Series of new N, N-dialkylphthalazine-1,4-dione derivatives were synthesized in two or three steps starting from 4-chlorophthalic anhydride. This versatile and efficient route, let to afford huge family of compounds that can be considered a useful intermediates for the preparation of new tricyclic compounds.

Experimental section

Preparation of 8-chloro-2-methyl-2,3-dihydrophthalazine-1,4-dione (1a) and 5-chloro-2-methyl-2,3-dihydrophthalazine-1,4-dione (1b).

The 4-chlorophtalic anhydride (5.48 mmol), methyl-hidrazine 98% (6.025mmol) and montmorillonite KSF clay (5 g) were mixed and grinded properly in a mortar, and placed in a clean and dry beaker. The reaction mixture was first preheated in a microwave oven for 15 minutes in periods of 1 minute each one (power 350 W) and the heating continued for 1 minute (power 450 W) and other minute (600 W) for completion of the reaction. The reaction mixture was cooled to the room temperature and the resulting product extracted with CH_2Cl_2/MeOH (9/1) (4 X 25 mL). The montmorillonite KSF clay was filtered off and the solvent removed by rotary. Compounds **1a** and **1b** were separated by HPLC ($CHCl_3$/iPrOH 2%).

Compound (**1a**). Yield: 62%. Melting point: 233ºC

Compound **(1b).** Yield: 34%. Melting point: 238ºC

Preparation of 2-(3-Bromopropyl)-8-chloro-3-methyl-2,3-dihydrophthalazine-1,4-dione (2b) and 2-(3-Bromopropyl)-5-chloro-3-methyl-2,3-dihydrophthalazine-1,4-dione (2d).

Compound (**1a**) or **(1b)** (2.37 mmol) and K_2CO_3 (7.12 mmol) were suspended en acetone (100mL). 1, 4-Dibromopropane (7.12 mmol) was added to the suspension and then the reaction mixture was stirred at room temperature for 24 hours. The K_2CO_3 was filtered off and the solvent removed by rotary. The crude product was purified by chromatography column (hexane/ ethylacetate 9/1 and 85/15).

Compound (**2b**). Yield: 85%. Melting Point: 115ºC

Compound (**2d**). Yield: 80%. Melting Point: 113ºC

Preparation of 2-(2-Bromoethyl)-5-chloro-3-methyl-2,3-dihydrophthalazine-1,4-dione (2c).

Compound (**1a**) (2.37 mmol) and K_2CO_3 (7.12 mmol) were suspended en acetone (100mL). 1, 4-Dibromoethane (7.12 mmol) was added to the suspension and the reaction mixture was stirred at room temperature for 24 hours. The K_2CO_3 was filtered off and the solvent removed by rotary. The crude product was purified by column chromatography (hexane/ ethylacetate 9/1 and 85/15) obtaining **2c**. Yield: 17%. Melting Point: 110ºC.

Preparation of 2-(3-Azidopropyl)-8-chloro-3-methyl-2,3-dihydrophthalazine-1,4-dione (3a) and 2-(3-Azidopropyl)-5-chloro-3-methyl-2,3-dihydrophthalazine-1,4-dione (3c)

Compound (**2b**) or (**2d**), sodium azide (3.48 mmol) and NaI (0.174 mmol) were suspended in DMSO. The reaction mixture was heated under reflux for 24h. The solvent was evaporated under vacuum and the crude product was purified by HPLC ($MeOH/H_2O$ (9/1).

Compound (**3a**). Yield: 70%. Melting Point: 61ºC

Compound (**3c**). Yield: 66%. Melting Point: 73ºC

Preparation of 2-(2-Azidoethyl)-5-chloro-3-methyl-2,3-dihydrophthalazine-1,4-dione. (3b)

Compound **(2c)** (1.57 mmol), sodium azide (3.48 mmol) and NaI (0.174 mmol) were suspended in DMSO. The reaction mixture was heated under reflux for 24h. The solvent was evaporated under vacuum and the crude product was purified by HPLC (MeOH/H_2O (9/1). Yield: 72%. Melting point: 112ºC.

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