Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2015, 7(4):257-261

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Nano TiO2: A recyclable catalyst for one pot synthesis of 2-(substituted phenyl) phthalazin-1(2*H*)-one

Vishal Lad[1], Jabbar G. Mulla[2], B. R. Agarwal[3] and Mazahar Farooqui[1,4*]

[1]Post Graduate and Research Center, Maulana Azad College, Aurangabad
[2]Adarsh Mahavidyalaya, Omerga Dist, Osmanabad, India
[3]J. E. S. College, Jalna, India
[4]Dr. Rafiq Zakaria College for Women, Aurangabad (MS), India

---

ABSTRACT

We have developed an efficient protocol for synthesis of 2-(substituted phenyl) phthalazin-1(2H)-ones from Phthalaldehydic acid, substituted phenyl hydrazine using Nano TiO2 as a catalyst. Simplicity, short reaction time, easy work up, cheap catalyst, good yield are the major advantages of the proposed method.

Keywords*:* Phthalazin-1(2*H*)-ones Phthalaldehydic acid Substituted phenyl hydrazine

---

INTRODUCTION

Developing new, simple synthetic methodologies for different heterocycles from readily available starting materials is an important task in organic synthesis. Three or four component one pot reactions have gained a considerable importance for the rapid and efficient synthesis of a wide variety of organic molecules [1,2]. These reactions have been investigated extensively in organic synthesis; mainly due to their ability to generate complex molecules from simple starting materials using one step reaction.

Phthalazinones are a group of condensed heterocycles having a significant biological activity. They are used to treat variety of disorders like diabetes [3,4], asthama[5,6,] hepatitis B [7], vascular hypertension [8,9] and arrhythmia [10.] They are also useful intermediate for the synthesis of inhibitors of vascular endothelial growth factor (VEGF)[11]. They also act as potent antimicrobial and inhibitors of poly(ADP-ribose)polymerase-1 [12.] Azelastine is a well known antiallergic and antihistaminic drug from the phthalazinones derivative.

Various methods for synthesis of phthalazinones are reported in the literature that includes cycloaddition [13-16], reduction [17,18,] cyclocondensation [19] and biotechnological approaches [20]. But usually these methods involve strong acid and bases, harsh reaction conditions longer reaction time etc. Considering the limitations of the reported methods, the need for the development of new method for the synthesis of phthalazinones is strongly desirable.

With our continued interest in developing methodologies for synthesis of biologically significant heterocyclic compounds, we are describing a new method for the synthesis of phthalazinones from phthadehydic acid and substituted phenyl hydrazines by using nano TiO2 as catalyst in ethanol with good yield.

EXPERIMENTAL SECTION

Phthalaldehydic acid, substituted phenyl hydrazines and Nano TiO_2 were purchased from commercial sources and used without further purification. The melting points were determined in open capillary tubes on a Buchi 530 melting point apparatus and are uncorrected. The homogeneity of the compounds was monitored by ascending thin layer chromatography (TLC) on silica gel-G (Merck) coated aluminum plates, visualized by iodine vapor. ^1H NMR spectra were recorded on a 400 MHz Varian-Gemini spectrometer and chemical shift reported in parts per million (ppm), using tetramethylsilane (TMS) as internal standard. Mass spectra were taken with Micromass-QUATTRO-II of WATER mass spectrometer.

General Procedure for 2-(substituted phenyl) phthalazin-1(2*H*)-one
To a mixture of phthalaldehydic acid (10 mmol), substituted phenyl hydrazine (10 mmol) and ethanol (15 ml), a catalytic amount (10 mol %) of Nano TiO_2 was added. The reaction mixture was refluxed for 20-30 min. On completion (monitored by TLC), the mixture was cooled and filtered. The crude product was recrystallised by using ethanol to get a pure product. All compounds from the series **3(a-j)** are prepared using the similar procedure. The physical data of the synthesized compounds is presented in Table 3.

3.1. 2-phenylphthalazin-1(2H)-one (3a)
^1H NMR (400 MHz, $CDCl_3$) δ ppm: 8.63–8.51 (m, 1 H, Aromatic), 8.42 (s,1 H, Aromatic), 7.76–7.14 (m, 8 H, Aromatic); MS *m/z*: 223 $[M+H]^+$.

3.2. 2-(4-methoxyphenyl)phthalazin-1(2H)-one (3j)
^1H NMR (400 MHz, $CDCl_3$) δ ppm: 8.58–8.44 (m, 1 H, Aromatic), 8.22 (s,1 H, Aromatic), 7.89–7.13 (m, 7 H, Aromatic), 3.68 (s, 3H, CH_3); MS *m/z*: 253 $[M+H]^+$.

RESULTS AND DISCUSSION

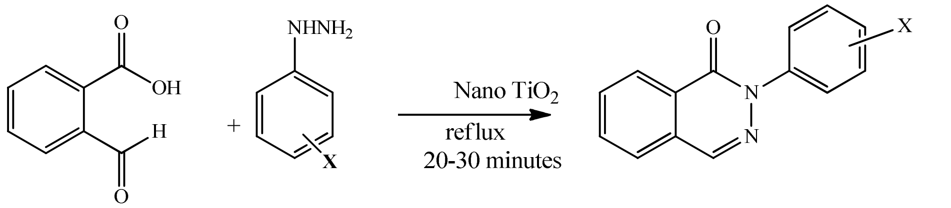
As a part of our program to find improved synthetic routes for the preparation of organic compounds [21,22,] herein we would like to report our investigation into an environmental friendly and highly efficient procedure for the synthesis of 2-(substituted phenyl)phthalazin-1(2H)-ones. The compounds were synthesized from phthalaldehydic acid and various substituted phenyl hydrazines in ethanol and by using Nano TiO_2 as a catalyst in good yield **(**Scheme 1**)**. To the best of our knowledge the synthesis of phthalazinones in ethanol using Nano TiO_2 as catalyst to accomplish such transformation has not been reported in the literature.

Effect of solvents
To find out the optimum reaction conditions, we have considered the synthesis of (**3a)**. Further we studied the effect of solvent on reaction kinetics and yield of product using Nano TiO2 as catalyst (50 mol %). A range of solvents such as acetonitrile, ethyl acetate, THF, toluene, dichloromethane, ethanol were examined (Table 1**)**. From the table it is observed that ethanol is more favorable for completion of reaction without any special efforts for isolation of product with good yield.

Effect of catalyst loading
The effect of catalyst loading on the yield of product is also investigated (Table 2). We carried the reaction for compound (**3a)** and used Nano TiO2at various load such as 50 mol %, 40 mol %, 30 mol %, 20 mol %, 10 mol % and 5 mol %. From the result it is observed that use of 10 mol % Nano TiO2 is more useful giving the product up to 98 % yield.

Catalyst Recycling
The catalyst has been recycled for 4 runs without significant loss of yields in the product.

Using optimized conditions, we extended the study further to explore the applicability of the Nano TiO2 catalyst for the synthesis 2-(substituted phenyl) phthalazin-1(2*H*)-one **3(a-j)**. The reaction proceeded smoothly under mild conditions and accommodated a wide range of phenyl hydrazines bearing both electron-donating and electron-withdrawing substituent.



1 **2** **3(a-j)**

Where X= H, Cl, Br, F, CH_3, OCH_3, NO_2

Scheme 1- Synthesis of 2-(substituted phenyl) phthalazin-1(2*H*)-ones

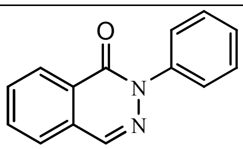
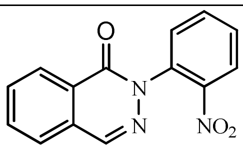
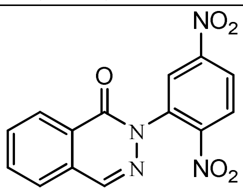
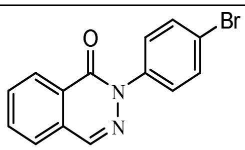
Table 1- Synthesis of 2-phenylphthalazin-1(2*H*)-one (3a) using Nano TiO_2 (50 mol %) in different solvents

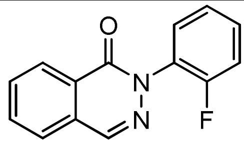
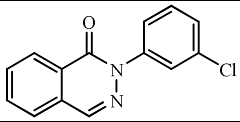
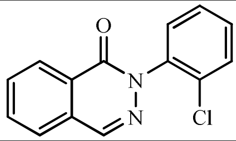
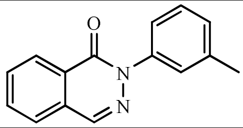
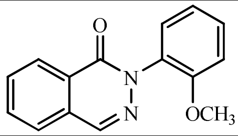
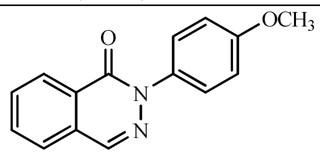
Sr. No.	Solvent	Temperature	Time (min)	Yield %
1	Acetonitrile	reflux	45	92
2	Ethyl acetate	reflux	60	90
3	THF	reflux	75	85
4	Toulene	reflux	100	70
5	Dichloromethane	reflux	90	75
6	Ethanol	reflux	20	98

Table 2- Effect of catalyst loading on the yield of 2-phenylphthalazin-1(2*H*)-one (3a) in ethanol

Sr. No.	Catalyst	Quantity (mole %)	Yield (%)
1	Nano TiO_2	50	98
2	Nano TiO_2	40	98
3	Nano TiO_2	30	98
4	Nano TiO_2	20	98
5	Nano TiO_2	10	98
6	Nano TiO_2	5	81

Table 3- Physical data of 2-(substituted phenyl) phthalazin-1(2*H*)-ones derivatives 3(a-j)

Entry	Compounds	Time (min)	Yield (%)	Melting point (°C)	
				Observed	Reported
3a		20	98	102-104	104-105 [23]
3b		30	95	206-208	204-206 [24]
3c		25	96	176-178	175-177 [25]
3d		20	98	166-168	168-169 [26]

3e		25	95	122-124	120.5-121.5 [23]
3f		30	96	136-138	135 [27]
3g		30	96	126-128	96 [28]
3h		20	98	48-50	48-50 [29]
3i		20	96	96-98	98-100 [29]
3j		25	98	104-106	105-107 [29]

CONCLUSION

In conclusion, we have developed a simple, efficient, ecofriendly method for the synthesis of biologically significant 2-(substituted phenyl)phthalazin-1(2*H*)-ones derivative **3(a-j)** from phthalaldehydic acid and phenyl hydrazine using Nano TiO2 as catalyst in ethanol. The highlighting advantages of this method include simplicity, low reaction time, easy work up, better yield (95-98%) compared with reported methods. This procedure will therefore be of general use and interest to the synthetic chemistry study.

REFERENCES

[1] Bashir Ahmad Dar and Mazahar Farooqui *Orbital Elec. J. Chem.,* **2011**;3(2): 89-93, 2011
[2] Bashir A. Dar, Nisar Ahmad, Jyoti Patial, Parveen Sharma, Kushal Bindu, Sudip Maity, Baldev Singh *J. Saudi Chem. Soc.* doi:10.1016/j.jscs.2011.09.015 (Available online)
[3] Mylari BL, Larson ER, Beyer TA, et al. *J. Med. Chem.* **1991;** 34: 108.
[4] Madhavan GR, Chakrabarti R, Kumar SKB, et al. *Eur. J. Med. Chem.* **2001**; 36: 627.
[5] Nakajima M, Ohyama K, Nakamura S, et al. *Drug. Metab. Dispos*. **1999**; 27: 792.
[6] Ukita T, Sugahara M, Terakawa Y, et al. *J. Med. Chem.* **1999;** 42: 1088.
[7] El Ashry ESH, Abdel-Rahman AAH, Rashed N, Rasheed HA. *Pharmazie*. **1999;** 54: 893.
[8] Garcia-Cadenas AE, Olmo E, Lopez JL, et al. *Aus. Chem. Soc.* and *Aus. Pharm. Soc***. 2005**; 138.
[9] Demirayak S, Karaburun C, Beis R. *Eur. J. Med. Chem.* **2004**; 39: 1089.
[10] Engel J, Kutscher B, Fleischhauer I, et al. EP 0590551; **1994.**
[11] Bold G, Altmann KH, Frei J, et al. *J. Med. Chem.* **2000;** 43: 2310.
[12] Cockcroft XK, Dillon J, Dixon L, et al. *Bioorg. Med. Chem. Lett.* **2006**; 16: 1040.
[13] Biniecki S, Moll M. PLP 60625; [*Chem. Abstr.,* **1970;** 74: 76435p].
[14] Raoul P. DEP 2045111; [*Chem. Abstr***., 1971**; 74: 141839p].
[15] Butula I, Ruzdija A, Kalmar J. *Croat. Chem. Acta***. 1979**; 52: 43.
[16] Matsushiro K, Miyashita M. JPP 49051287; [*Chem. Abstr.,* **1974**; 81: 169555p].

[17] Sato H, Horie S, Sekikawa N, Ono H. DEP 2632656; [*Chem. Abstr.*, **1977***; 86*: 171487p].
[18] Hirayama T, Kamada M. JPP 52027785; [*Chem. Abstr.*, 1977; 87: 184540p].
[19] Sutherland JB, Freeman JP, Williams AJ. *Appl. Microbiol. Biotechnol*. **1998**; 49: 445.
[20] Sugimoto A, Sakamoto K, Fujino Y, Takashima Y, Ishikawa M. *Chem. Pharm. Bull*. **1985**; 33**: 2809**.
[21] Sangshetti JN, Kokare ND, Shinde DB. *Rus. J. Org. Chem***. 2009**; 45: 1116-1118.
[22] Darandale SN, Sangshetti JN, Shinde DB. *J. Kor. Chem. Soc***.** **2012**; 56: 328.