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Green Procedure for the Synthesis of Phthalazino[2,3-b]phthalazine-5,7,12,14tetraones

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Abstract: Different novel phthalazino[2,3-*b*]phthalazine-5,7,12,14-tetraones were synthesized in a simple and environmentally benign method from the reaction of phthalic anhydrides with semicarbazide or thiosemicarbazide using montmorillonite K-10 clay as solid heterogeneous acidic catalyst and microwaves under solvent-free conditions in good yields and short reaction times. Products were characterized by the elemental analysis, IR, NMR, and mass spectrometry.

Keywords: microwave, montmorillonite K-10 clay, phthalic anhydrides, semicarbazide, solvent-free condition, thiosemicarbazide

In the past few decades, the synthesis of new heterocyclic compounds has been a subject of great interest because of their wide applicability. Heterocyclic compounds occur very widely in nature and are essential to life. Nitrogen-containing heterocyclic molecules constitute the largest portion of

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chemical entities, which are part of many natural products, fine chemicals, and biologically active pharmaceuticals and are vital for enhancing the quality of life.^[1-4] In this connection, various studies on fused nitrogen heterocycles have been reported,^[5-13] but a limited number of phthalazino[2,3-*b*]phthalazine-5,7,12,14-tetraone derivatives have been synthesized.^[14–17] Most of these procedures involve the use of corrosive reagents such as polyphosphoric and acetic acids, and the reported yields are far from satisfactory. Therefore, the use of inexpensive and environmentally safe solid acids would extend the scope of these transformations.

Recently, the use of solid acidic catalysts such as clays, zeolites, and ionexchange resins has received much interest in different areas of organic synthesis because of their environmental compatibility, reusability, greater selectivity, noncorrosiveness, low cost, and ease of handling. Particularly, the clay catalysts make the reaction process more convenient, economic, and environmentally benign and act as both Brønsted and Lewis acids in their natural and ion-exchanged forms, enabling them to function as efficient catalysts for various transformations.^[18]

Montmorillonite clays have been used as catalysts for a number of organic reactions and offer several advantages over classical acids: strong acidity, noncorrosive properties, recyclability, cheapness, mild reaction conditions, high yields and selectivity, and ease of setup and workup.^[19–23]

In the past few years, a growing interest has been shown in the use of microwave irradiation in organic synthesis.^[24–26] Microwave-assisted organic reactions constitute an emerging technology that makes experimentally and industrially important organic syntheses more effective and more ecofriendly than the conventional reactions.^[27–29] In addition, microwave-mediated solvent-free synthesis offers advantages for reducing hazardous explosions and the removal of the high boiling solvents from the reaction mixtures.^[30,31]

RESULTS AND DISCUSSION

In continuation of our study with microwaves on solid surfaces, $[^{32-34}]$ herein we describe a convenient and simple method to synthesize some of the new phthalazino[2,3-*b*]phthalazine-5,7,12,14-tetraones from the reaction of different substituted phthalic anhydrides as well as either semicarbazide or thiosemicarbazide reacted for the appropriate time under solvent-free conditions and microwave irradiation on montmorillonite K-10 clay (Scheme 1).

The polarity of the carbonyl group of semicarbazide is greater than its thio-carbonyl analogs in thiosemicarbazide, so the $-NH_2$ group of thiosemicarbazide is a better nucleophile than the $-NH_2$ group of semicarbazide and hence the more yields will be obtained.

The nature of the substituents on the aromatic ring of phthalic anhydride has different influences. For instance, presence of electron-withdrawing

Phthalazino[2,3-b]phthalazine-5,7,12,14-tetraones



Scheme 1. Synthesis of phthalazino[2,3-b]phthalazine-5,7,12,14-tetraones.

groups such as chlorine, nitro, and fluorine, which increase the polarity of the carbonyl group inductively, gives high yields of products as well as short reaction times compared to those of the unsubstituted rings.

IR spectral evaluations of the obtained compounds showed that in the cases of **c**, **e**, **h**, and **j**, 1,11-disubstituted compound is a real product (and not 1,8-), whereas in the cases of **d** and **i**, 2,10-disubstituted compound (and not 2, 9-) was obtained.

The use of clay as an efficient heterogeneous acidic catalyst as well as microwave irradiation offer high yields of products compared to the conventional procedures, probably due to the more molecular interactions. The related comparative data have been shown in the typical procedure section.^[17]

All attempts to prepare the products in the absence of montmorillonite K-10 clay failed (despite 20 min of irradiation at 180°C, 900 W). So, the role of montmorillonite K-10 clay as a solid catalyst in this reaction is important and essential.

In summary, we have described a new, simple, and highly efficient procedure for the synthesis of phthalazino[2,3-*b*]phthalazine-5,7,12,14-tetraone compounds using montmorillonite K-10 clay. The catalyst is inexpensive, nontoxic, and reusable, which makes the process convenient and economically viable. The recyclability of the K-10 clay, which is another advantage of our method, has been explained in the footnote of Table 1.

EXPERIMENTAL

Melting points were measured on an Electro-thermal 9100 apparatus. The IR spectra were obtained on a Perkin-Elmer FT IR GX instrument in KBr discs. The ¹H NMR and ¹³C NMR spectra were recorded on a FT-NMR Jeol FX 90Q spectrometer using TMS as internal standard (δ /ppm). Mass spectra were measured with GCMS-Agilent 5973 N instrument. Elemental analyses were performed using a Heraeus CHN-Rapid analyzer. Chemicals were purchased from the Aldrich, Merck, and Fluka chemical companies and used without further purification. The chemical composition (average

Entry	Anhydride	Reagent	Compound ^a	Optimum time (min)	Yield $(\%)^b$	
					Fresh clay	Recovered clay
1	Phthalic anhydride	Semicarbazide	а	7.0	61	54
2	Tetrachloro-phthalic anhydride	Semicarbazide	b	3.5	73	64
3	3-Nitro-phthalic anhydride	Semicarbazide	с	5.5	69	60
4	4-Nitro-phthalic anhydride	Semicarbazide	d	5.0	67	57
5	3-Fluoro-phthalic anhydride	Semicarbazide	е	6.0	65	58
6	Phthalic anhydride	Thiosemicarbazide	f	5.0	67	61
7	Tetrachloro-phthalic anhydride	Thiosemicarbazide	g	3.0	82	77
8	3-Nitro-phthalic anhydride	Thiosemicarbazide	h	4.0	74	58
9	4-Nitro-phthalic anhydride	Thiosemicarbazide	i	3.5	73	56
10	3-Fluoro-phthalic anhydride	Thiosemicarbazide	j	4	70	64

Table 1. Yields and reaction times of compounds \mathbf{a} -j

^{*a*}Compound $\mathbf{a} = \mathbf{f}$ is known and its spectra and physical data has been reported in the literature.^[17]

^bYields are after recrystallization. The applied K-10 clay was filtered off after completion of the reaction, washed with methanol, and dried in vacuum to be reused in the subsequent reactions, which showed gradual decrease in the activity.

Notes: $\mathbf{a} = \mathbf{f}$) Phthalazino[2,3-*b*]phthalazine-5,7,12,14-tetraone. $\mathbf{b} = \mathbf{g}$) 1,2,3,4,8,9,10,11-Octachlorophthalazino[2,3-*b*]phthalazine-5,7,12,14-tetraone $\mathbf{c} = \mathbf{h}$) 1,11-Dinitrophthalazino[2,3-*b*]phthalazine-5,7,12,14-tetraone $\mathbf{d} = \mathbf{i}$) 2, 9-Dinitrophthalazino[2,3-*b*]phthalazine-5,7,12,14-tetraone $\mathbf{e} = \mathbf{j}$) 1,11-Diffuorophthalazino[2,3-*b*]phthalazine-5,7,12,14-tetraone.

D.

value) of the applied montmorillonite K-10 clay [surface area: $200 \text{ m}^2/\text{g}$; pH: 2.5–3.5) is 73.0% SiO₂, 14.0% Al₂O₃, 2.7% Fe₂O₃, 0.2% CaO, 1.1% MgO, 0.6% Na₂O, and 1.9% K₂O.

General Procedure for the Synthesis of Phthalazino[2,3b]phthalazine-5,7,12,14-tetraones

In a typical experiment, phthalic anhydride (2.2 mmol, 0.330 g), thiosemicarbazide (1 mmol, 0.091 g), and montmorillonite K-10 clay (1 g) are mixed, ground properly, placed in a septum-capped microwave tube, and irradiated at 180°C (900 W) for a certain period of time (5 min). After completion of the reaction, which was monitored by thin-layer Chromatography (TLC) using n-hexane-acetone as eluent, the mixture was allowed to cool to the room temperature. The resulting product was extracted into dichloromethane $(2 \times 20 \text{ mL})$ and filtered off, and the solvent was removed by rotary. The obtained product [(phthalazino[2,3-b]phthalazine-5,7,12,14-tetraone (f)] was washed with distilled water very well, dried in an oven, and recrystallized from acetic acid. Mp $\sim 340^\circ C,~67\%$ yield, 0.195 g (with fresh K-10 clay) and 61% yield, 0.178 g (with recovered K-10 clay) (lit.: mp 343-344°C, 55% yield, reaction time 1.5 h using poly-phosphoric acid^[17]). The solid clay portion was washed with methanol and dried at 120°C under reduced pressure to be reused in the subsequent reactions, which showed gradual decrease in the activity (Table 1). The physical as well as the spectral data of known compound $(\mathbf{a} = \mathbf{f})$ was found to be identical with the authentic sample. Unknown compounds ($\mathbf{b} = \mathbf{g}, \mathbf{c} = \mathbf{h}, \mathbf{d} = \mathbf{i}$, and $\mathbf{e} = \mathbf{j}$) were characterized by the elemental analysis, IR, NMR, and mass spectrometry.

Data

Phthalazino[2,3-*b*]phthalazine-5,7,12,14-tetraone (entries 1 and 6, Table 1, a = f). Mp 332–336°C. m/z: 292 (M^+). IR (KBr) ν : 3092.7, 1853.5, 1792.6, 1763.5, 1686.4, 1597.4, 1471.3, 1258.7, 1109.8, 907.2. ¹H NMR (DMSO- d_6) δ : 7.81–7.98 (8H, m, Ar). ¹³C NMR (DMSO- d_6) δ : 123.0, 129.3, 134.8, 168.9. Anal. calcd. for C₁₆H₈N₂O₄ (%): C, 65.76; H, 2.76; N, 9.58. Found: C, 65.12; H, 2.60; N, 9.48.

1,2,3,4,8,9,10,11-Octachlorophthalazino[2,3-b]phthalazine-5,7,12,14-

tetraone (entries 2 and 7, Table 1, b = g). Mp $317-321^{\circ}$ C. m/z: 568 (M^{+}). IR (KBr) ν : 1846.7, 1835.4, 1775.7, 1757.76, 1373.9, 1299.3, 1233.8, 923.3. ¹³C NMR (DMSO- d_6) δ : 170.24, 139.92, 135.46, 127.41. Anal. calcd. for C₁₆Cl₈N₂O₄ (%): C, 33.80; N, 4.92. Found: C, 33.67; N, 4.53.

1,11-Dinitrophthalazino[**2,3-***b*]**phthalazine-5,7,12,14-tetraone** (entries **3** and **8**, Table **1**, c = h). Mp 271–274°C. m/z: 382 (M^+). IR (KBr) ν : 3172.9, 3026.24, 2922.0, 1669.9, 1654.7, 1618.0, 1603.3, 1578.1, 1560.2,

1560.8, 1491.6, 1336.5, 1298.2, 825.6. ¹H NMR (DMSO- d_6) δ : 7.92–8.63 (6H, m, Ar). ¹³C NMR (DMSO- d_6) δ : 167.71, 167.43, 148.45, 136.85, 133.39, 132.70, 132.52, 129.61. Anal. calcd. for C₁₆H₆N₄O₈ (%): C, 50.26; H, 1.57; N, 14.56. Found: C, 50.14; H, 1.38; N, 14.33.

2,9-Dinitrophthalazino[**2,3**-*b*]**phthalazine**-**5,7,12,14-tetraone** (entries **4** and **9**, **Table 1**, **d = i**). Mp 263–267°C. m/z: 382 (M^+). IR (KBr) ν : 3106.3, 3006.5, 1641.8, 1626.7, 1598.7, 1539.9, 1466.6, 1355.1, 1188.4, 1061.3, 791.9. ¹H NMR (DMSO- d_6) δ : 8.36–8.94 (6H, m, Ar). ¹³C NMR (DMSO- d_6) δ : 162.52, 162.43, 154.81, 137.78, 134.66, 133.19, 129.26, 122.34. Anal. calcd. for C₁₆H₆N₄O₈ (%): C, 50.26; H, 1.57; N, 14.56. Found: C, 50.09; H, 1.29; N, 14.25.

1, 11-Difluorophthalazino[2,3-*b*]phthalazine-5,7,12,14-tetraone (entries 5 and 10, Table 1, e = j). Mp 298–302°C. *m/z*: 328 (*M*⁺). IR (KBr) ν : 3021.9, 2921.0, 1671.2, 1664.3, 1618.1, 1603.1, 1577.8, 1572.2, 1560.2, 1491.3, 1336.6, 1299.7, 825.8. ¹H NMR (DMSO-*d*₆) δ : 7.82–8.27 (6H, m, Ar). ¹³C NMR (DMSO-*d*₆) δ : 175.27, 163.66, 163.32, 163.08, 136.42, 136.27, 130.52. Anal. calcd. for C₁₆H₆ F₂N₂O₄ (%): C, 58.53; H, 1.82; N, 8.53. Found: C, 58.34; H, 1.69; N, 8.21.

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