Solvent-free organic salt media mono symmetrical aza-Michael: synthesis of new N-mono substituted phthalhydrazide derivatives

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ABSTRACT

In this paper, C–N bond formation between 2,3-dihydrophthalazine-1(4H),4-dione (phthalhydrazide) and α,β-unsaturated esters was investigated and a new series of phthalazine derivatives was synthesized using an efficient and simple method under solvent-free conditions. An aza-Michael addition of phthalhydrazide to both acrylic and fumaric esters led to N-mono-substituted phthalhydrazides (as mono-Michael adduct) in the presence of tetrabutylammonium bromide as a high polar media, and 1,4-diaza-bicyclo[2,2,2]octane as an available organic base. In this reaction, the N1,N2-bis-Michael adduct was not observed at all. Also, reactions were performed at 90°C and yields of products were good to excellent.

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Phthalhydrazide; phthalazine derivatives; Michael addition; α,β-unsaturated esters; solvent-free conditions; mono-Michael adduct

Introduction

Nitrogen-containing heterocycles have a wide range of biological properties such as antibiotics, fungicides, anti-HIV protease, plant growth regulators, anti-thrombotic agents, anti-cancer, anti-inflammatory, anti-allergic, analgesic, glucagon receptor antagonism, herbicides, insecticides (1–9) and cytotoxic agents (10). Among a large variety of nitrogen-containing heterocycles, those containing a phthalazine moiety show some pharmacological and biological properties (11). Phthalazine derivatives have been reported to possess anticonvulsant (12), cardiotonic (13), vasorelaxant (14), cytotoxic (3), antimicrobial (15), antifungal (5), anti-cancer (6) and anti-inflammatory properties (7). In addition, these compounds show good promise as new luminescence materials and fluorescence probes (16). Therefore, it is not surprising that many synthetic methods have been developed for the synthesis of different derivatives of phthalazines. In one of these methods, 2,3-dihydrophthalazine-1(4H),4-dione (“phthalhydrazide”) is used. This compound is commonly used as an intermediate in the synthesis of many molecules with a phthalazine moiety (17–22).

Although there are many reports of the synthesis of phthalazine derivatives (23–27), their broad utility range has accentuated the need to develop newer methods and the synthesis of novel derivatives of these compounds. Herein, in line with our interest in the aza-Michael addition reaction of amides and imides to α,β-unsaturated esters and the scientific interest in this method (28–36), and also in continuation of our previous work on the synthesis of nitrogen-containing heterocyclic compounds, using the Michael addition reaction of 4-phenylurazole to α,β-unsaturated esters (37,38), we decided to synthesize a new collection of biologically active compounds. Recently, we reported the synthesis of N1,N2-disubstituted 4-phenylurazole derivatives by Michael addition of this symmetric Michael donor to diverse acrylic esters (37). Also, we reported the reaction between
4-phenylurazole and symmetric fumaric esters that led to produce an unexpected product (38). In order to extend these reactions to other similar symmetrical Michael donors, herein, we report the addition of 2,3-dihydropthalazin-1(4H),4-dione (phthalhydrazide) to αβ-unsaturated esters under solvent-free conditions (Scheme 1).

**Experimental**

Phthalhydrazide and αβ-unsaturated esters were synthesized according to literature procedures (39,40). Esters were transferred via syringe. Organic solvents were removed under reduced pressure by a rotary evaporator. Reactions were monitored by thin-layer chromatography (TLC) carried out on silica-gel plates (SILG/UV 254, Merck) using UV light as the visualizing agent. Chromatography was performed on Merk 60 silica gel (230–240 mesh) with n-hexane and ethyl acetate mixture (80:20) as eluent. FT-IR spectra were recorded on a Perkin-Elmer RX-1 instrument. Elemental analysis for C, H and N was performed using a Heraeus CHN-O-Rapid analyzer. 1H NMR and 13C NMR spectra were recorded mostly on a Bruker 400 MHz instrument. The melting points were determined in open capillaries with a Stuart Melting Point Apparatus and remained uncorrected. Chemical shifts were recorded in ppm downfield from tetramethylsilane. J values were given in Hz. Abbreviations used in 1H NMR are s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet).

**General procedure for the Michael addition of phthalhydrazide to αβ-unsaturated esters**

A well-ground mixture of phthalhydrazide (1.0 mmol), DABCO (1.0 mmol) and TBAB (1.0 mmol) was placed in a flask. αβ-Unsaturated ester (1.2 mmol) was added to this mixture and the flask was heated in the oil bath. When the oil bath temperature reached 90°C, a brown solution was formed. After keeping the reaction flask at this temperature for the stipulated time (Table 3), the reaction was completed as monitored by TLC. Then, the flask was allowed to cool down to room temperature and chloroform (20 mL) was added. The solution was stirred to dissolve all the solids. TBAB was recovered by the addition of water (3 x 20 mL) to this solution and then collected and dried under vacuum. The chloroform layer was washed with water (3 x 15 mL). After dried with sodium sulfate and the removal of the organic solvent, the residue was purified on short silica-gel column with n-hexane/ethyl acetate (8:2) as the eluent.

**Butyl 3-(1,4-dioxo-3,4-dihydropthalazin-2(1H)-yl)propanoate (3c):** White Solid, mp 101–103°C. 1H NMR (400 MHz, CDCl3): δ ppm 0.88 (t, 3H, J = 6.8 Hz), 1.32 (sextet, 2H, J = 7.4 Hz), 1.58 (quintet, 2H, J = 6.8 Hz), 2.86 (t, 2H, J = 6.8 Hz), 4.11 (t, 2H, J = 6.7 Hz), 4.38 (t, 2H, J = 6.8 Hz), 7.80–7.84 (m, 2H), 8.09–8.12 (m, 1H), 8.38–8.42 (m, 1H); 13C NMR (100 MHz, CDCl3): δ ppm 12.6, 55.5; Anal. Calcd. for C15H18N2O4: C, 66.00; H, 6.56; N, 9.65. Found: C, 66.18; H, 6.56; N, 9.21.

**Hexyl 3-(1,4-dioxo-3,4-dihydropthalazin-2(1H)-yl)propanoate (3d):** White Crystal, mp 96–98°C. 1H NMR (400 MHz, CDCl3): δ ppm 0.87 (t, 3H, J = 6.8 Hz), 1.24–1.32 (m, 6H), 1.58 (quintet, 2H, J = 6.7 Hz), 2.86 (t, 2H, J = 6.9 Hz), 4.10 (t, 2H, J = 6.7 Hz), 4.39 (t, 2H, J = 6.9 Hz), 7.80–7.85 (m, 2H), 8.09–8.13 (m, 1H), 8.39–8.43 (m, 1H), 9.48 (s, 1H); 1H NMR (100 MHz, CDCl3): δ ppm 12.9, 21.4, 24.5, 27.4, 30.3, 32.1, 44.1, 64.2, 121.4, 123.3, 126.3, 128.4, 131.8, 132.0, 151.3, 156.7, 171.0; IR (KBr, cm−1): 3099, 2955, 1736, 1647, 1571, 1438, 1375, 1251, 1094, 784, 688, 555; Anal. Calcd. for C15H19N2O4: C, 64.13; H, 6.97; N, 8.80. Found: C, 63.85; H, 6.56; N, 9.21.

**Ethylhexyl 3-(1,4-dioxo-3,4-dihydropthalazin-2(1H)-yl)propanoate (3e):** Yellow Solid, mp 82–84°C. 1H NMR (400 MHz, CDCl3): δ ppm 0.81–0.87 (m, 6H), 1.22–1.28 (m, 6H), 1.28–1.33 (m, 2H), 1.52 (quintet, 1H, J = 6.0 Hz), 2.88 (t, 2H, J = 7.2 Hz), 4.02 (dd, 2H, J1 = 10.9 Hz, J2 = 6.0 Hz), 4.41 (t, 2H, J = 7.2 Hz), 7.80–7.85 (m, 2H), 8.09–8.12 (m, 1H), 8.42–8.44 (m, 1H); 1H NMR (100 MHz, CDCl3): δ ppm 9.8, 12.9, 21.8, 22.6, 27.8, 28.6, 29.2, 32.0, 37.5, 44.2, 66.4, 124.0, 124.2, 126.2, 128.4, 131.8, 132.0, 151.5, 156.8, 170.9; IR (KBr, cm−1): 3061, 2929, 1733, 1646, 1562, 1461, 1380, 1244, 1094, 786, 687, 555; Anal. Calcd. for C19H24N2O4: C, 65.87; H, 7.56; N, 8.09. Found: C, 66.18; H, 7.30; N, 8.47.

**Butyl 3-(1,4-dioxo-3,4-dihydropthalazin-2(1H)-yl)-2-methylpropanoate (3g):** Yellow viscous oil. 1H NMR (400 MHz, CDCl3): δ ppm 0.82 (t, 3H, J = 7.4 Hz), 1.20–1.28 (m, 5H), 1.47–1.56 (m, 2H), 3.13 (sextet, 1H, J = 7.1 Hz), 4.07 (td, 2H, J1 = 6.6 Hz, J2 = 1.8 Hz), 4.28 (d, 2H, J = 6.6 Hz), 7.81–7.85 (m, 2H), 8.09–8.13 (m, 1H), 8.40–8.43 (m, 1H); 13C NMR (100 MHz, CDCl3): δ ppm 12.5, 13.6, 18.0, 29.2, 37.6, 50.5, 63.8, 123.9, 124.2, 126.3, 128.4, 131.7, 131.9, 151.3, 157.0, 174.1; IR (KBr, cm−1):...
Dipropyl 2-(1,4-dioxo-3,4-dihydrophthalazin-2(1H)-yl)succinate (3f): Orang viscous oil. 1H NMR (400 MHz, CDCl3): δ ppm 0.78 (t, 3H, J = 6.9 Hz), 0.81 (t, 3H, J = 7.0 Hz), 1.16–1.29 (m, 8H), 1.52–1.61 (m, 4H), 3.11 (dd, 1H, J1 = 16.6 Hz, J2 = 6.1 Hz), 4.01–4.22 (m, 4H), 5.94 (dd, 1H, J1 = 8.1 Hz, J2 = 6.1 Hz), 7.80–7.84 (m, 2H), 7.98–8.01 (m, 1H), 8.40–8.43 (m, 1H); 13C NMR (100 MHz, CDCl3): δ ppm 12.8, 12.9, 21.1, 21.2, 26.8, 26.9, 27.0, 27.1, 33.7, 55.8, 64.3, 65.1, 123.3, 123.4, 126.5, 128.0, 131.5, 132.2, 149.4, 157.4, 168.1, 169.7; IR (KBr, cm−1): 3080, 2958, 1733, 1646, 1584, 1467, 1379, 1261, 1093, 782, 695, 489; Anal. Calcd. for C22H30N2O6: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.55; H, 7.46; N, 6.21.

Diethyl 2-(1,4-dioxo-3,4-dihydrophthalazin-2(1H)-yl)succinate (3g): Orang viscous oil. 1H NMR (400 MHz, CDCl3): δ ppm 0.74–0.88 (m, 6H), 1.13–1.19 (m, 6H), 1.20–1.24 (m, 2H), 1.25–1.28 (m, 2H), 1.29–1.43 (m, 2H), 1.45–1.55 (m, 2H), 3.04–3.13 (m, 1H), 3.22–3.29 (m, 1H), 4.88–5.01 (m, 2H), 5.91–5.98 (m, 1H), 7.77–7.84 (m, 2H), 7.95–7.97 (m, 1H), 8.42–8.45 (m, 1H); 13C NMR (100 MHz, CDCl3): δ ppm 14.7, 14.8, 19.4, 19.5, 20.6, 20.7, 36.1, 38.7, 38.8, 57.9, 72.8, 73.9, 125.4, 128.4, 130.0, 133.3, 134.0, 151.4, 159.4, 169.8, 171.3; IR (KBr, cm−1): 3081, 2960, 1733, 1647, 1584, 1458, 1379, 1260, 1120.
Dicyclohexyl 2-(1,4-dioxo-3,4-dihydrophthalazin-2(1H)-yl)succinate (3r): Orang viscous oil. \(^{1}\)HNMR (1H)-yl)succinate (3r): \(J = 8.0\) Hz, 3.26 (dd, 1H, \(J = 16.4\) Hz, \(J = 3.7\) Hz), 4.85 (septet, 1H, \(J = 3.7\) Hz), 5.94 (t, 1H, \(J = 7.0\) Hz), 7.77–7.83 (m, 2H), 7.94–7.98 (m, 1H), 8.41–8.45 (m, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) ppm 22.2, 22.3, 22.5, 24.1, 24.2, 30.1, 30.2, 30.3, 34.1, 56.0, 72.5, 73.3, 123.4, 123.5, 126.3, 127.9, 131.3, 131.4, 149.6, 157.4, 167.6, 169.2; IR (KBr, cm\(^{-1}\)): 3081, 2934, 1729, 1660, 1588, 1450, 1360, 1258, 1013, 783, 695, 485; Anal. Calcd. for C\(_{22}\)H\(_{30}\)N\(_2\)O\(_6\): C, 63.14; H, 6.83; N, 6.33. Found: C, 65.54; H, 7.12; N, 6.71.

**Results and discussion**

Considering the above reports and our interest in applying the solvent-free system conditions, we first investigated phthalhydrazide 1 to ethyl acrylate 2b as the model reaction, in the presence of TBAB and various organic and inorganic bases to evaluate their capabilities and selectivity (Scheme 2). In our initial study, we found that mono-substituted phthalhydrazide (mono-Michael adduct) 3b was the only product and no di-substituted phthalhydrazide (bis-Michael adduct) 4 was produced at all. The steric hindrance of the first alkyl group (at N1 or N2 atoms) prevents the addition of the second alkyl group. We tried to perform the reaction with twice the amount of ethyl acrylate to obtain bi-Michael adduct, but observed that mono-Michael adduct was the exclusive product of the reaction. These results indicated that in this reaction, the steric effects outweigh the electronic effects, so that further alkylation does not tend to occur. Among the tested bases, the best result was obtained when DABCO was used as base in the model reaction and afforded good yield of 85% after 10 h (Table 1, entry 9). Due to this advantage, base DABCO was chosen for our model reaction. The reaction failed in the presence of NaOH and KOH (Table 1, entries 6,7). Other tested bases and no base media (Table 1, entries 1,2,4,5,8) had little effect, and produced a low yield of mono-Michael adduct. Also, \(\text{K}_2\text{CO}_3\) as an inorganic base afforded product 3b in moderate yield of 60% (Table 1, entry 3).

In another study, we investigated the effect of different solvents on this reaction (Table 2). In this study, we observed that when TBAB was used instead of solvent, mono-Michael adduct was obtained in a good yield (Table 2, entry 10). The model reaction failed in most organic solvents, for example DMF, \(\text{CH}_3\text{Cl}_2\), MeOH, \(\text{CH}_3\text{CO}_2\text{Et}\) and \(\text{H}_2\text{O}\) (Table 2, entries 1, 4, 5, 8, 9) at their boiling points. After refluxing for 10 h, a trace amount of mono-Michael adduct was obtained in \(\text{CHCl}_3\) and \(\text{EtOH}\) (Table 2, entries 3,6). Also, a low yield of product 3b was afforded in DMSO, acetone and no solvent media (Table 2, entries 2,7,11).

Next, we optimized the amount of phthalhydrazide, ethyl acrylate, TBAB and DABCO. The best result was obtained with 1.0 mmol of phthalhydrazide, TBAB, DABCO and 1.2 mmol of ethyl acrylate. With the optimized reaction conditions in hand, the scope and limitation of reaction were explored using phthalhydrazide and a variety of acrylic esters. The results are summarized in Table 3 (Table 3, entries 1–7).

It is seen from the results in Table 3 that the reaction with acrylic esters proceeded smoothly and afforded the corresponding products in good to excellent yields. Also, it was observed that the bulky alkoxy groups (~OR) of the acrylic esters did not have a significant effect on the reaction yields and times under the model reaction conditions (Table 3, entries 2–5, 7).

| Entry | Base\(^a\) | Time (h) | Yield (%)\(^b\) |
|-------|------------|----------|-----------------|
| 1     | None       | 10       | 10              |
| 2     | \(\text{Na}_2\text{CO}_3\) | 10       | Trace           |
| 3     | \(\text{K}_2\text{CO}_3\) | 10       | 60              |
| 4     | \(\text{NET}_3\) | 10       | 5               |
| 5     | Pyridine   | 10       | 10              |
| 6     | \(\text{NaOH}\) | 10       | –               |
| 7     | KOH        | 10       | Trace           |
| 8     | \(\text{Sr}_2\text{CO}_3\) | 10       | –               |
| 9     | DABCO      | 10       | 85              |

| Entry | Solvent\(^a\) | Time (h) | Yield (%)\(^b\) |
|-------|----------------|----------|-----------------|
| 1     | DMF            | 10       | –               |
| 2     | DMSO           | 10       | 10              |
| 3     | \(\text{CHCl}_3\) | 10       | Trace           |
| 4     | \(\text{CH}_3\text{Cl}_2\) | 10       | –               |
| 5     | MeOH           | 10       | –               |
| 6     | \(\text{EtOH}\) | 10       | Trace           |
| 7     | \(\text{CH}_3\text{CO}_2\text{Et}\) | 10       | 5               |
| 8     | \(\text{CH}_3\text{CO}_2\text{Et}\) | 10       | –               |
| 9     | \(\text{H}_2\text{O}\) | 10       | –               |
| 10    | TBAB           | 10       | 85              |
| 11    | No solvent     | 10       | 5               |

\(^a\)Phthalhydrazide (1.0 mmol), base (1.0 mmol), TBAB (1.0 mmol) and ethyl acrylate (1.2 mmol) at 90°C.

\(^b\)Isolated yield.

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**Table 1.** Aza-Michael reaction of phthalhydrazide with ethyl acrylate in the presence of various bases and TBAB under solvent-free conditions.

| Entry | Base\(^a\) | Time (h) | Yield (%)\(^b\) |
|-------|------------|----------|-----------------|
| 1     | None       | 10       | 10              |
| 2     | \(\text{Na}_2\text{CO}_3\) | 10       | Trace           |
| 3     | \(\text{K}_2\text{CO}_3\) | 10       | 60              |
| 4     | \(\text{NET}_3\) | 10       | 5               |
| 5     | Pyridine   | 10       | 10              |
| 6     | \(\text{NaOH}\) | 10       | –               |
| 7     | KOH        | 10       | Trace           |
| 8     | \(\text{Sr}_2\text{CO}_3\) | 10       | –               |
| 9     | DABCO      | 10       | 85              |

\(^a\)Phthalhydrazide (1.0 mmol), base (1.0 mmol), TBAB (1.0 mmol) and ethyl acrylate (1.2 mmol) at 90°C.

\(^b\)Isolated yield.
Table 3. Aza-Michael addition of phthalhydrazide 1 to α,β-unsaturated esters 2 under solvent-free conditions.

| Entry | Ester 2 | Product 3 | Time (h) | Yield (%)<sup>a</sup> |
|-------|---------|-----------|----------|----------------------|
| 1     | ![2a](image) | –         | 120      | –                    |
| 2     | ![2b](image) | ![3b](image) | 10       | 85                   |
| 3     | ![2c](image) | ![3c](image) | 10       | 90                   |
| 4     | ![2d](image) | ![3d](image) | 10       | 90                   |
| 5     | ![2e](image) | ![3e](image) | 10       | 85                   |
| 6     | ![2f](image) | –         | 120      | –                    |
| 7     | ![2g](image) | ![3g](image) | 12       | 80                   |

<sup>a</sup> Determined by NMR and/or elemental analysis.
| Entry | Ester 2 | Product 3 | Time (h) | Yield (%) |
|-------|---------|-----------|----------|-----------|
| 8     | ![2h](image) | 120 | -        | -         |
| 9     | ![2i](image) | ![3i](image) | 15 | 80       |
| 10    | ![2j](image) | ![3j](image) | 15 | 75       |
| 11    | ![2k](image) | ![3k](image) | 15 | 70       |
| 12    | ![2l](image) | ![3l](image) | 15 | 70       |
| 13    | ![2m](image) | ![3m](image) | 15 | 70       |

(Continued)
| Entry | Ester 2 | Product 3 | Time (h) | Yield (%) |
|-------|---------|-----------|----------|-----------|
| 14    | ![Image](image1.png) | 2n | – | 120 | – |
| 15    | ![Image](image2.png) | 2o | 18 | 65 |
| 16    | ![Image](image3.png) | 2p | 18 | 70 |
| 17    | ![Image](image4.png) | 2q | 18 | 60 |
| 18    | ![Image](image5.png) | 2r | 20 | 60 |
| 19    | ![Image](image6.png) | 2s | – | 120 | – |

(Continued)
Table 3. Continued.

| Entry | Ester 2 | Product 3 | Time (h) | Yield (%)^a |
|-------|---------|-----------|----------|-------------|
| 20    | ![Image](103x644) | –         | 120      | –           |
| 21    | ![Image](102x648) | –         | 120      | –           |
| 22    | ![Image](102x485) | –         | 120      | –           |

^aIsolated yields.

Scheme 1. General method for the Michael addition of phthalhydrazide to α,β-unsaturated esters under solvent-free conditions.
donor structures. Instead of 4-phenylurazole, phthalhydrazide was heated with ethyl fumarate in the presence of DABCO and TBAB (Scheme 3). However, only mono-Michael adduct was afforded and bis-Michael adduct or expected product was not obtained at all. This difference in behavior between 4-phenylurazole and phthalhydrazide with fumaric esters can be ascribed to the fact that the carbon atom of the carbonyl group in 4-phenylurazole is more reactive than the one in phthalhydrazide. Next, we investigated the generality of this reaction with other fumaric esters (Table 3, entries 8–22).

From Table 3, it is clear that generally, in the reaction in which alkoxy fumarates were employed, the corresponding mono-Michael adducts were produced in moderate to good yields within 15–20 h (Table 3, entries 9–13 and 15–18). However, when benzyloxy fumarates were employed as Michael acceptors, the TLC test did not show any progress in the reaction, even after a long time of 120 h (Table 3, entries 20–22). These results can be attributed to the increased steric hindrance of the Michael acceptors. The existence of hindered –OR groups on fumaric esters make them a weak Michael acceptor and hence, addition is much more difficult. Whereas the addition to cyclohexyl fumarate (bearing large –OR groups) provided a relatively low yield of product (Table 3, entries 18), the addition of Michael donor to linear fumaric esters, for example ethyl, propyl, butyl, penty and hexyl fumarate afforded the related mono-substituted phthalhydrazide in good yields (Table 3, entries 9–13). However, when octyl fumarate was employed as a Michael acceptor, reactivity was low and no product was observed in the TLC test because of the long chain alkoxy group n-octyloxy (Table 3, entry 14). It is important to note that when \(\alpha,\beta\)-unsaturated esters containing small alkoxy groups were used as Michael acceptors, the desired Michael adducts were not obtained and the related carboxylic acids of the employed esters resulted as the only product of these reactions (Table 3, entries 1,6,8). We believe that these \(\alpha,\beta\)-unsaturated esters are more susceptible to hydrolysis due to their smaller alkoxy groups (–OMe) under the reaction conditions. Also, it was interesting that in the case of 2-methoxyethyl fumarate, the reaction was unsuccessful (Table 3, entry 19). This can be attributed to methoxy group at 2-position of the alkoxy moiety of this ester. Due to the electronegative oxygen atom at the 2-position of this moiety, the bond length is decreased and, consequently, a condensed Michael acceptor is provided that the nucleophilic attack becomes difficult on it.

**Conclusions**

In summary, we developed a novel, effective, clean, and environment-friendly procedure for the synthesis of new phthalazine derivatives in the presence of TBAB as a high polar media under solvent-free conditions. It was found that among the various organic and inorganic bases, DABCO was a more suitable base and mono-substituted phthalhydrazide (as mono-Michael adduct) was the sole product of the reaction. Also, we observed that in this reaction when fumaric esters were used as Michael acceptors, the structure of the alkoxy group had a significant effect on the reaction yield and time.

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Disclosure statement
No potential conflict of interest was reported by the authors.

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