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Reaction of phthalhydrazide and acetylenedicarboxylates in the presence of N-heterocycles: an efficient synthesis of phthalazine derivatives

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ABSTRACT

Some new phthalazine derivatives were prepared by reaction of phthalhydrazide and dialkyl acetylenedicarboxylates in the presence of N-heterocycles.

1. Introduction

N-Heterocycles have received considerable attention in the literature as a consequence of their exciting biological properties and their role as pharmacophores.[1] For example, quinoline and imidazole ring systems are important structural units found in various naturally occurring alkaloids and synthetic analogues with interesting biological properties.[2,3] Similarly, heterocycles containing the phthalazine moiety are of interest because they show some pharmacological and biological activities.[4–6] Phthalazine derivatives were reported to possess anticonvulsant,[7] cardiotonic[8] and vasorelaxant[9] activities. Therefore, a number of methods have been reported for the synthesis of phthalazine derivatives.[7,10–16] Despite the available methods, the development of new synthetic methods for the efficient preparation of heterocycles containing a phthalazine ring fragment is therefore an interesting challenge.

The reaction of nucleophiles with activated acetylenes has attracted the attention of organic chemists for a long time, especially from the vantage point of heterocyclic synthesis.[17] Of special interest in this area is the reaction of nitrogen-containing heterocycles with activated acetylenes, which has been the subject of significant research.[18] An interesting example is the reaction between isoquinoline, dimethyl acetylenedicarboxylate and amides, in which the corresponding isoquinolinyl-2-butenedioate derivatives were isolated.[19]

Considering the above reports, and our interest in the synthesis of heterocyclic compounds,[20–27] herein, we describe a simple synthesis of dihydrophthalazin-2(1*H*)-yl-fumarate derivatives.

Our studies were initiated by the reaction of phthalhydrazide **1** with dimethyl acetylenedicarboxylate (DMAD) **2a** or diethyl acetylenedicarboxylate (DEAD) **2b** in the presence of isoquinoline **3**, which proceeded smoothly at ambient temperature in acetone to afford dialkyl 2-(1-(1,4-dioxo-3,4-dihydrophthalazin-2(1*H*)-yl) isoquinolin-2(1*H*)-yl)fumarates **4a**,**b** in good yields after 24 h (Scheme 1). However, when this reaction was carried out with di-*tert*-butyl acetylenedicarboxylate (DTAD) **2c**, the TLC and ^{1}H NMR spectra of the reaction mixture showed a combination of starting materials and numerous products; the expected product was obtained in only trace amount.

Mechanistically, it is reasonable that the reaction involves initial formation of a 1:1 zwitterionic intermediate[19] **5** between isoquinoline **3** and the dialkyl acetylenedicarboxylate **2**. This intermediate is protonated by phthalhydrazide **1** and then attacked by the conjugate base of phthalhydrazide to produce **4** (Scheme 2).

In view of the success of the above reaction, we explored the use of *N*-methylimidazole **6** as a third component. Reaction of phthalhydrazide **1** with DMAD in the presence of *N*-methylimidazole **6** in acetone led to the formation of the corresponding dimethyl 2-(2-(1,4-dioxo-3,4-dihydrophthalazin-2(1*H*)-yl)-3-methyl-2,3-dihydro-1*H*-imidazol-1-yl)fumarate **7** in 62% yield (Scheme 3). Surprisingly, when DEAD or DTAD was used in this reaction, a different result was obtained under the same conditions affording

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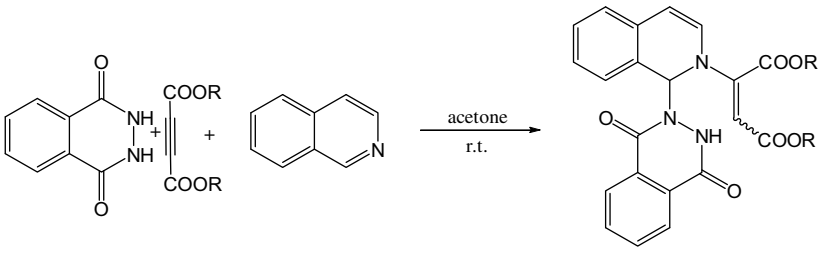
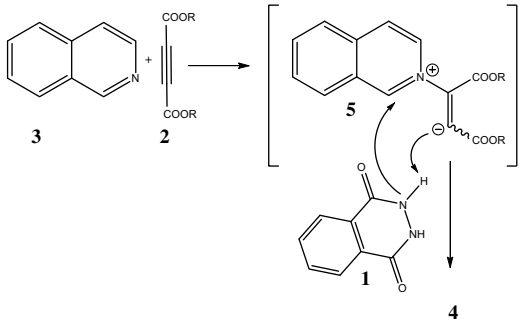


1 2a-c 3 4a-c

Product	R	Time (h)	yield (%)
4a	Me	24	76
4b	Et	24	70
4c	*t*-Bu	48	Trace

Scheme 1.



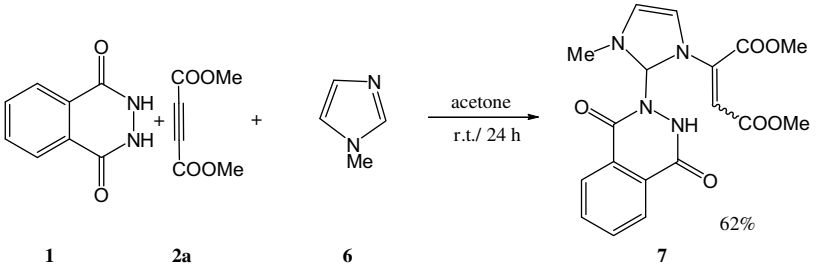
Scheme 2.

other classes of heterocycles, such as alkyl-2-(1-methyl-6,8,13-trioxo-1,8,13,14a-tetrahydroimidazo [2′,1′:3,4][1,2,4]triazino-[1,2-*b*]phthalazin-5(6*H*)-ylidene) ethanoate derivatives **8b,c** (Scheme 4).

It should be noted that under similar conditions, the reaction of phthalhydrazide **1** with DMAD or DEAD in the presence of quinoline **9** led to dialkyl 2-(1,4-dioxo-3,4-dihydrophthalazin-2(1*H*)-yl) fumarates **10a**,**b** (Scheme 5). When the same reaction was carried out with DTAD, the expected product was obtained only in trace amount after 48 h.

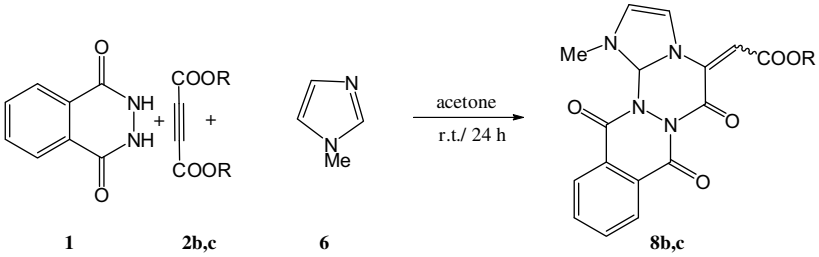
To illustrate the role of quinoline **9**, the reaction of phthalhydrazide **1** with DMAD was studied in the absence of quinoline. The product was obtained only in trace amount under these conditions after 48 h.

It is reasonable to assume that product **10** results from initial addition of quinoline to the dialkyl acetylenedicarboxylate **2** and subsequent protonation of the 1,3-dipolar intermediate **11**, by phthalhydrazide **1**. Then, the resulting positively charged ion **12** could be attacked by the conjugate base of phthalhydrazide to produce the nitrogen ylide **13**, which undergoes a proton-transfer reaction to produce **14**. The intermediate **14** is then converted to **10** by elimination of quinoline (Scheme 6).



1 2a 6 7

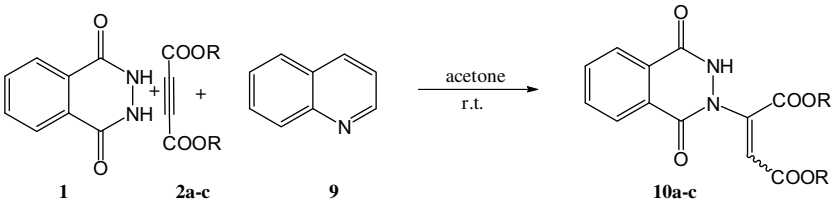
Scheme 3.



1 2b,c 6 8b,c

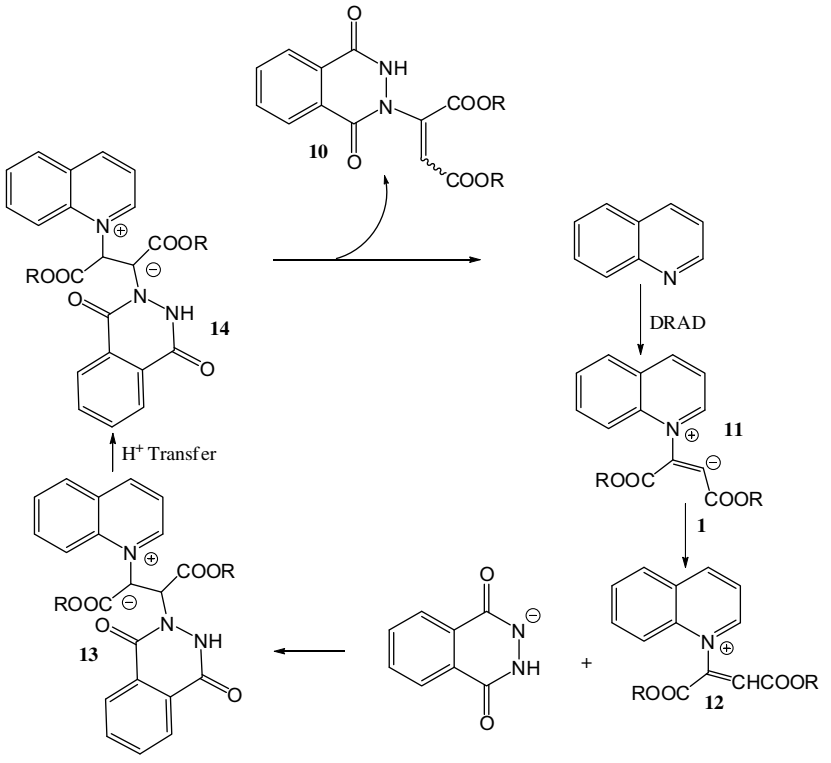
Product	R	yield (%)
8b	Et	65
8c	*t*-Bu	55

Scheme 4.



Product	R	Time (h)	yield (%)
10a	Me	24	67
10b	Et	24	72
10c	*t*-Bu	48	Trace

Scheme 5.



Scheme 6.

Compounds **4**, **7**, **8** and **10** are stable solids whose structures were established by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis.

In summary, the reaction between phthalhydrazide and dialkyl acetylenedicarboxylate in the presence of N-heterocycles gave new phthalazine derivatives in good yields.

2. Experimental

2.1. General procedure for the preparation of compounds 4, 7, 8 and 10

To a magnetically stirred solution of phthalhydrazide (1 mmol) and N-heterocycle (1 mmol) in acetone (10 ml) was added dropwise a mixture of the appropriate dialkyl acetylenedicarboxylate (1 mmol) in acetone (2 ml) at room temperature for 10 min. The reaction mixture was stirred for 24 h. The solvent was removed under reduced pressure. The residue was washed with ether (5 ml) and recrystallized from acetone/*n*-hexane (1:3) to afford the pure product.

2.2. Dimethyl 2-(1-(1,4-dioxo-3,4-dihydrophthalazin-2(1*H*)-yl)isoquinolin-2(1*H*)-yl)fumarate (4a)

Yellow powder (76%); mp: 306 °C dec. IR (KBr) (ν_{max}/cm^{-1}): 3436, 1741, 1656, 1589. MS (EI, 70 eV) *m*/*z* (%): 272 ($M^{+}-C_8H_6N_2O_2$, 5), 245 (10), 162 (20), 129 (100), 75 (45). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 3.70 (3H, s, CH_3), 3.79 (3H, s, CH_3), 6.34 (1H, s, *CH*═C), 6.63–8.51 (10H, m, H-Ar), 9.31 (1H, s, *CH*N_2), 12.34 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 53.0, 57.6, 121.5, 124.8, 124.9, 127.0, 127.1, 128.4, 128.5, 131.9, 133.1, 134.3, 136.0, 141.6, 150.7, 152.0, 158.3, 168.1. Anal. Calcd for $C_{23}H_{19}N_3O_6$: C, 63.74; H, 4.42; N, 9.70. Found: C, 63.80; H, 4.37; N, 9.63.

2.3. Diethyl 2-(1-(1,4-dioxo-3,4-dihydrophthalazin-2(1*H*)-yl)isoquinolin-2(1*H*)-yl)fumarate (4b)

Light yellow powder (70%); mp: 123–125 °C. IR (KBr) (ν_{max}/cm^{-1}): 3430, 2994, 1709, 1674, 1621. MS (EI, 70 eV) *m*/*z* (%): 460 ($M^{+}-1$, 5), 431 (20), 300 (10), 287 (80), 259 (100), 76 (65). ^{1}H

NMR (300 MHz, DMSO-d_6): δ_H 1.22 (3H, t, J = 7.5 Hz, CH_3), 1.26 (3H, t, J = 7.6 Hz, CH_3), 4.15 (2H, q, J = 7.1 Hz, CH_2), 4.24 (2H, q, J = 7.0 Hz, CH_2), 6.61 (1H, s, *CH*=C), 6.61–8.51 (10H, m, H-Ar), 9.31 (1H, s, *CH*N_2), 12.27 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 13.7, 14.1, 60.7, 62.1, 110.9, 121.4, 124.8, 125.4, 126.5, 127.8, 127.9, 128.1,128.6, 128.7, 131.3, 132.4, 133.9, 136.3, 140.7, 144.5, 151.4, 152.6, 158.2, 163.4, 165.5. Anal. Calcd for $C_{25}H_{23}N_3O_6$: C, 65.07; H, 5.02; N, 9.11. Found: C, 65.12; H, 5.07; N, 9.05.

2.4. Dimethyl 2-(2-(1,4-dioxo-3,4-dihydrophthalazin-2(1*H*)-yl)-3-methyl-2,3-dihydro-1*H*-imidazol-1-yl)fumarate (7)

Cream powder (62%); mp: 148–150 °C. IR (KBr) (ν_{max}/cm^{-1}): 3427, 3076, 1731, 1629. MS (EI, 70 eV) m/z (%): 386 (M^+, 5), 355 (43), 226 (25), 76 (100). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 3.15 (3H, s, CH_3), 3.61 (3H, s, CH_3), 3.67 (3H, s, CH_3), 6.33 (1H, s, *CH*=C), 6.74 (1H, s, *CH*N_2), 7.93–8.28 (6H, m, H-Ar and 2CH), 12.04 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 49.0, 53.0, 57.5, 120.8, 124.9, 125.3, 125.7, 127.1, 128.4, 128.6, 137.9, 133.2, 134.4, 150.7, 158.3, 168.1 Anal. Calcd for $C_{18}H_{18}N_4O_6$: C, 55.96; H, 4.70; N, 14.50. Found: C, 55.90; H, 4.75; N, 14.57.

2.5. Ethyl 2-(1-methyl-6,8,13-trioxo-1,8,13,14a-tetrahydroimidazo[2′,1′:3,4][1,2,4]triazino[1,2-*b*] phthalazin-5(6*H*)-ylidene)ethanoate (8b)

Light yellow powder (65%); mp: 170 °C dec. IR (KBr) (ν_{max}/cm^{-1}): 3114, 1738, 1654. MS (EI, 70 eV) m/z (%): 368 (M^+, 10), 332 (15), 259 (100), 76 (80). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 0.74 (3H, br s, CH_3), 3.63 (3H, s, CH_3), 3.90 (2H, br s, CH_2), 6.34 (1H, s, *CH*=), 6.89 (1H, s, CHN_2), 7.10–8.28 (6H, m, H-Ar and 2CH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 13.8, 33.2, 57.6, 61.7, 120.9, 124.8, 125.1, 127.0, 128.5, 128.6, 133.1, 134.3, 138.3, 150.9, 158.3, 167.7. Anal. Calcd for $C_{18}H_{16}N_4O_5$: C, 58.69; H, 4.38; N, 15.21. Found: C, 58.75; H, 4.42; N, 15.27.

2.6. *tert*-Butyl 2-(1-methyl-6,8,13-trioxo-1,8,13,14a-tetrahydroimidazo[2′,1′:3,4][1,2,4]triazino[1,2-*b*] phthalazin-5(6*H*)-ylidene)ethanoate (8c)

Cream powder (55%); mp: 196 °C dec. IR (KBr) (ν_{max}/cm^{-1}): 3141, 3103, 1745, 1642. MS (EI, 70 eV) m/z (%): 395 (M^+−1, 5), 368 (25), 259 (35), 231 (100). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.18 (9H, s, 3CH_3), 3.85 (3H, s, CH_3), 6.53 (1H, s, *CH*=), 6.76 (1H, s, *CH*N_2), 7.14–8.42 (6H, m, H-Ar and 2CH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 27.46, 33.3, 59.5, 81.88, 121.0, 124.7, 125.2, 127.0, 128.2, 128.8, 132.9, 134.1, 138.3, 150.7, 158.2, 166.9. Anal. Calcd for $C_{20}H_{20}N_4O_5$: C, 60.60; H, 5.09; N, 14.13. Found: C, 60.54; H, 5.14; N, 14.21.

2.7. Dimethyl 2-(1,4-dioxo-3,4-dihydrophthalazin-2(1*H*)-yl)fumarate (10a)

Cream powder (67%); mp: 181 °C dec. IR (KBr) (ν_{max}/cm^{-1}): 3436, 1730, 1666. MS (EI, 70 eV) m/z (%): 304 (M^+, 6), 245 (100), 130 (19), 76 (50). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 3.70 (3H, s, CH_3), 3.79 (3H, s, CH_3), 6.63 (1H, s, *CH*=C), 7.30–8.34 (4H, m, H-Ar), 12.27 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 52.4, 52.9, 111.1, 125.1, 125.6, 127.5, 128.3, 133.6, 135.1, 144.1, 152.2, 157.7, 163.1, 165.4. Anal. Calcd for $C_{14}H_{12}N_2O_6$: C, 55.27; H, 3.98; N, 9.21. Found: C, 55.21; H, 3.94; N, 9.27.

2.8. Diethyl 2-(1,4-dioxo-3,4-dihydrophthalazin-2(1*H*)-yl)fumarate (10b)

Cream powder (72%); mp: 295 °C dec. IR (KBr) (ν_{max}/cm^{-1}): 3105, 1727, 1654. MS (EI, 70 eV) m/z (%): 287 (M^+−OEt, 20), 259 (40), 104 (100), 76 (100). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 0.96 (3H, br s, CH_3), 1.20 (3H, br s, CH_3), 4.03–4.24 (4H, m, CH_2), 6.89 (1H, s, *CH*=C), 7.94–8.23 (4H, m, H-Ar), 12.04 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C14.0, 14.3, 61.2, 62.5, 124.9, 125.5, 125.8, 127.0, 128.3, 133.2, 134.6, 140.5, 151.2, 157.7, 162.7, 163.3. Anal. Calcd for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 4.85; N, 8.43. Found: C, 57.78; H, 4.80; N, 8.35.

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