Green synthesis of novel (E)-2-(1,4-dioxo-1,2,3,4-tetrahydropthalazine-2-carbonyl)-3-(1H-indol-3-yl)acrylonitriles

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Green synthesis of novel title compounds (6) has been developed from 3-(1,4-dioxo-3,4-dihydraphthalazine-(1H)-yl)-3-oxopropanenitrile (3) and indole-3-aldehyde (4) using Knoevenagel condensation followed by alkylation with alkylation agents. Compound 6 could also be synthesised by alkylation of 4 followed by condensation with 3. In an alternate sequence of reactions, 6 could be synthesised either from treatment of 3 with N,N-dimethylformamide dimethyl acetal to form (E)-3-(dimethlamino)-2-(1,4-dioxo-1,2,3,4-tetrahydropthalazine-2-carbonyl)acrylonitrile (8) followed by reaction with 10 or by the reaction 8 with 9 followed by alkylation.

Keywords: green chemistry; ethanol; L-proline; DMF-DMA

Introduction

Heterocycles containing the phthalazine moiety are of interest because they show some pharmacological and biological activities (1–13). Mogilaiah et al. (14) reported the synthesis of 1,8-naphthyridine-3-carbonylphthalazine-1,4-diones by the condensation of 1,8-naphthyridine-3-carboxylic acid hydrazides with phthalic anhydride using p-Toluenesulfonic acid (PTSA) as a catalyst under solid state conditions. Mogilaiah et al. (15) also reported the microwave irradiation of a mixture of 3-aryl-2-hydrazino-1,8-naphthyridines with phthalic anhydride in the presence of a catalytic amount of DMF resulting in 2-(3-aryl-1,8-naphthyridin-2-yl)-1,2,3,4-tetrahydropthalazine-1,4-diones.

Indole derivatives continue to receive much attention in organic synthesis because of their biological activities (16–21). Among them, 3-Substituted indole is one of the ‘privileged medicinal scaffold’, found in many biologically active compounds and natural products (22, 23). Through appropriate functional group modifications, these scaffolds are capable of providing ligands for a number of functionally and structurally discrete biological receptors. 3-Substituted indole scaffolds are found in a number of biologically active compounds especially with anticancer, anti-tumour (24), hypoglycemic, anti-inflammatory, analgesic and anti-pyretic activities (25, 26).

Keeping in view the potential importance of the phthalazine and indole ring containing compounds and in continuation of our earlier work on reactions of phthalic anhydride with nucleophiles (27–29), we now wish to report our studies on reactions of phthalic anhydride with hydrazide derivatives and their further modifications.

Results and discussion

As shown in Scheme 1, treatment of phthalic anhydride (1) with ethyl cyanohydrazide (2) in acetic acid at room temperature (RT) for 30 min resulted in the formation of 3-(1,4-dioxo-3,4-dihydrophthalazin-(1H)-yl)-3-oxopropanenitrile (3) whose structure was assigned on the basis of its spectral data (for details, please see the Experimental section). Compound 2 required in this work, was obtained (30) from the commercially available ethyl cyanoacetate by reaction with hydrazine hydrate in ethanol at 0–10°C for 15–20 min.

Scheme 1. Synthesis of 3 from 1 and 2.
An interesting observation was made here that in the $^1$H NMR spectrum of 3 the -NH- proton appeared at δ 11.2 as slightly broadened weak peak after integrating and the -CH$_2$- proton signal appeared at δ 4.1 as a sharp singlet. Both these signals disappeared from the spectrum on addition of D$_2$O to the solution. The exchange of -NH- proton with deuterium is well-known but the -CH$_2$- protons exchange with deuterium in the absence of any added base is unusual. In the present case, this may be due to the fact that the -CH$_2$- protons form an enol with adjoining -CO- leading to the formation of a six-membered chelate 3A as shown below:

![Diagram](image_url)

Condensation of 3 (1 mmol) with indole-3-aldehyde 4a (1 mmol) in ethanol containing the green catalyst L-proline (1mmol) for 30 min at RT gave (E)-2-(1,4-dioxo-1,2,3,4-tetrahydropthalazine-2-carbonyl)-3-(1H-indol-3-yl)acrylonitriles 5a in 85% yield on simple work-up of reaction mixture (Table 1, entry 1). The gross structure of this product was assigned on the basis of its spectral data (for details, please see the Experimental section). Furthermore, the compound was assigned E-configuration on the presumption that bulky groups in a transposition would confer thermal stability on the molecule. This has been found to be case by a careful examination of the framework molecular models of both E and Z configurations of 5a wherein it was observed that there were a minimum number of steric interactions in the E configuration.

The above reaction was examined by carrying out the condensation of 3 with 4a in the presence of different catalysts (piperidine, pyridine, triethylamine and L-proline) in different solvents (ethanol, methanol and dimethyl sulfoxide [DMSO]) at RT (Table 1). However, the condensation of 3 with 4a using L-proline as a catalyst at RT for 30 min in EtOH gave the best yield (85%) of 5a in pure form as seen by thin layer chromatography (TLC) and melting point (M.P; Table 1, entry 1). For finding out the optimum concentration of L-proline, the reaction was carried out by changing the amount of L-proline as a catalyst (Table 2). Results indicated that with 30 mol% (0.3 mmol) L-proline as a catalyst at RT for 30 min in EtOH gave best yield (85%) (Table 2, entry 4).

Reaction of 5a with dimethyl sulphate in triethanolamine at 80°C for 90 min gave 6a. The structure of this product was assigned on the basis of its spectral data (for details, please see the Experimental section). This reaction too was examined in different solvents containing different bases (Table 3). However, reaction in triethanolamine without any base at 80°C for 90–95 min gave best yield (85%) of 6a of good quality (TLC & M.P) (Table 3, entry 4).

After having optimised the reaction conditions, the generality of the reaction was confirmed by carrying out the condensation of 3 with 4a–4c using 30 mol% (0.3 mmol) L-proline as a catalyst at RT for

| Table 1. Effect of solvent, catalyst and temperature on reaction of 3 with 4a at RT yielding 5a. |
|---|---|---|---|
| Entry | Solvent | Catalyst | Time (hours) | 5a (%) |
| 1 | Ethanol | L-proline | 30 | 85 |
| 2 | Ethanol | Piperidine | 30 | 70 |
| 3 | Ethanol | Pyridine | 35 | 65 |
| 4 | Ethanol | Triethylamine | 40 | 55 |
| 5 | Methanol | Piperidine | 35 | 70 |
| 6 | Methanol | Pyridine | 35 | 65 |
| 7 | Methanol | Triethylamine | 45 | 60 |
| 8 | Methanol | L-proline | 35 | 75 |
| 9 | DMSO | Piperidine | 35 | 50 |
| 10 | DMSO | Pyridine | 40 | 45 |
| 11 | DMSO | Triethylamine | 45 | 40 |
| 12 | DMSO | L-proline | 35 | 40 |

| Table 2. The effect of amount of L-proline in the preparation of 5a by 3 with 4a in EtOH. |
|---|---|---|---|
| Entry | Solvent | Mol % of L-Proline | Time (hours) | 5a (%) |
| 1 | Ethanol | – | 12 | – |
| 2 | Ethanol | 10 | 3 | 70 |
| 3 | Ethanol | 20 | 2 | 75 |
| 4 | Ethanol | 30 | 1 | 85 |
| 5 | Ethanol | 50 | 1 | 85 |
| 6 | Ethanol | 100 | 1 | 85 |

| Table 3. Effect of solvent and temperature on reaction of 5a with dimethyl sulphate yielding 6a. |
|---|---|---|---|
| Entry | Solvent | Temperature | Time (hours) | 6a (%) |
| 1 | DMF/K$_2$CO$_3$/TBAB | RT | 2 | 75 |
| 2 | CH$_3$CN/K$_2$CO$_3$/TBAB | RT | 3 | 75 |
| 3 | PEG-600 | 80 | 2 | 75 |
| 4 | Triethanolamine | 80 | 1 | 85 |
| 5 | PEG-600 | 100 | 1.5 | 80 |
| 6 | Triethanolamine | 100 | 1 | 75 |
30–40 min in EtOH giving 5a–5c in good yields. The latter on alkylation of 5a–5c with alkylation agents in triethanolamine at 80°C for 90–100 min gave the corresponding indole-NH-alkylated derivatives 6a–6o. Using this strategy, alternatively, 6a–6o were prepared by alkylation of 4a–4c with alkylation agents in triethylamine at 80°C for 90–100 min to form 7a–7o followed by Knoevenagel condensation of the initial product with 3 using 30 mol % (0.3 mmol) L-proline as a catalyst at RT for 30 min in EtOH. All the above reactions are summarised in Scheme 2.

Alternatively, condensation of 3 with N,N-Dimethylformamide dimethyl acetal (DMF-DMA) for 10 min at RT gave (E)-3-(dimethlamino)-2-(1,4-dioxo-1,2,3,4-tetrahydrophthalazine-2-carbonyl)acrylonitrile 8. The latter on reaction with simple indoles 9 leading to 5 followed by alkylation with alkylation agents such as dimethyl sulfide (DMS), diethyl sulfide (DES), butylbromide, benzyl chloride and benzene sulphonyl chloride in triethanolamine at 80°C for about 2 h resulted in the formation of 6 (Scheme 3). In an alternate sequence of reactions, 8 on condensation directly with N-alkylindoles (N-methyl and N-benzyl) 10 in acetic acid at 100°C for 1–2 h leading to the formation of 6 (Tables 4–7).

Scheme 2. Synthesis of 6a–6l.

Scheme 3. Synthesis of 6a–6l.
Conclusion

In summary, we have successfully developed syntheses of novel (E)-2-(1,4-dioxo-1,2,3,4-tetrahydropthalazine-2-carbonyl)-3-(1H-indol-3-yl)acrylonitriles (6) under green conditions without formation of any by-products. The overall of products yields are very good.

Experimental section

Melting points are uncorrected and were determined in open capillary tubes in sulphuric acid bath. TLC

Table 4. Reaction times and yields of 5a–5c.

| Entry | Starting material used | Product | Time (min) | Yield a |
|-------|------------------------|---------|------------|---------|
| 1     | 3 4a (X = H)           | 5a      | 30         | 85      |
| 2     | 3 4b (X = Br)          | 5b      | 45         | 85      |
| 3     | 3 4c (X = NO2)         | 5c      | 45         | 83      |
| 4     | 8 9a (X = H)           | 5a      | 30         | 85      |
| 5     | 8 9b (X = Br)          | 5b      | 20         | 85      |
| 6     | 8 9c (X = NO2)         | 5c      | 30         | 85      |

aYields of crude products only.

Table 5. Reaction times and yields of 6a–6o.

| Entry | Starting material used | Alkylating agent | Product | Time (min) | Yield a |
|-------|------------------------|------------------|---------|------------|---------|
| 1     | 5a (X = H)             | DMS              | 6a      | 90         | 83      |
| 2     | 5a (X = H)             | DES              | 6b      | 90         | 80      |
| 3     | 5a (X = H)             | n-C4H9Br         | 6c      | 60         | 84      |
| 4     | 5a (X = H)             | PhCH2Cl          | 6d      | 90         | 85      |
| 5     | 5a (X = H)             | PhSO2Cl          | 6e      | 60         | 80      |
| 6     | 5b (X = Br)            | DMS              | 6f      | 120        | 75      |
| 7     | 5b (X = Br)            | DES              | 6g      | 90         | 70      |
| 8     | 5b (X = Br)            | n-C4H9Br         | 6h      | 90         | 75      |
| 9     | 5b (X = Br)            | PhCH2Cl          | 6i      | 120        | 85      |
| 10    | 5b (X = Br)            | PhSO2Cl          | 6j      | 90         | 80      |
| 11    | 5c (X = NO2)           | DMS              | 6k      | 120        | 83      |
| 12    | 5c (X = NO2)           | DES              | 6l      | 90         | 85      |
| 13    | 5c (X = NO2)           | n-C4H9Br         | 6m      | 120        | 80      |
| 14    | 5c (X = NO2)           | PhCH2Cl          | 6n      | 90         | 85      |
| 15    | 5c (X = NO2)           | PhSO2Cl          | 6o      | 90         | 80      |

aYields of crude products only.

Table 6. Reaction times and yields of 6a–6o.

| Entry | Starting material used       | Alkylating agent | Product | Time (min) | Yield a |
|-------|------------------------------|------------------|---------|------------|---------|
| 1     | 7a (X = H, R = CH3)         | 3                | 6a      | 30         | 85      |
| 2     | 7b (X = H, R = C2H5)        | 3                | 6b      | 45         | 79      |
| 3     | 7c (X = H, R = C4H9)        | 3                | 6c      | 30         | 78      |
| 4     | 7d (X = H, R = CH2-Ph)      | 3                | 6d      | 30         | 80      |
| 5     | 7e (X = H, R = SO2-Ph)      | 3                | 6e      | 30         | 85      |
| 6     | 7f (X = Br, R = CH3)        | 3                | 6f      | 45         | 83      |
| 7     | 7g (X = Br, R = C2H5)       | 3                | 6g      | 30         | 85      |
| 8     | 7h (X = Br, R = C4H9)       | 3                | 6h      | 45         | 80      |
| 9     | 7i (X = Br, R = CH2-Ph)     | 3                | 6i      | 30         | 85      |
| 10    | 7j (X = Br, R = SO2-Ph)     | 3                | 6j      | 30         | 82      |
| 11    | 7k (X = NO2, R = CH3)       | 3                | 6k      | 30         | 80      |
| 12    | 7l (X = NO2, R = C2H5)      | 3                | 6l      | 20         | 78      |
| 13    | 7m (X = NO2, R = C4H9)      | 3                | 6m      | 20         | 79      |
| 14    | 7n (X = NO2, R = CH2-Ph)    | 3                | 6n      | 30         | 80      |
| 15    | 7o (X = NO2, R = SO2-Ph)    | 3                | 6o      | 30         | 85      |

aYields of crude products only.
was run on silica gel – G and visualisation was done using iodine or UV light. IR spectra were recorded using Perkin – Elmer 1000 instrument in KBr pellets. $^1$H NMR spectra were recorded in DMSO – d$_6$ using TMS as internal standard using 400 MHz spectrometer. Mass spectra were recorded on Agilent-LCMS instrument. Starting materials 1, 4a–4c and 9a–9c were obtained from commercial sources and used as such.

Preparation of 3
A mixture of 1 (10 mmol), 2 (10 mmol) and acetic acid (20 mL) was stirred at RT for 30 min. At the end of this period, a colourless solid separated out of the reaction mixture and was collected by filtration. The insoluble solid was washed with hexane (10 mL) and then dried. The crude product was recrystallized from ethanol solvent to obtain 3.

3: mp: 150–1522°C; IR (KBr): 3293–3518 cm$^{-1}$ (broad, medium, -NH-), 1748 cm$^{-1}$ (sharp, strong, -CO-), 1682 cm$^{-1}$ (sharp, strong, -CO- of amide group); $^1$H- NMR (DMSO-d$_6$, 400 MHz): δ 4.2 (s, 2H, CH$_2$), 7.9–8.0 (m, 4H, Ar-H), 11.1 (s, 1H, -NH, D$_2$O exchangeable); 13C-NMR (DMSO-d$_6$, 400 MHz): δ 31.6, 36.9, 114.8, 124.8, 131.1, 136.2, 164.1, 164.8, 166.1; M$^+$+1 = 230.

Preparation of 5 from 3 and 4
A mixture of 3 (10 mmol), 4 (10 mmol), L-proline and EtOH (20 mL) was stirred at RT for 40–60 min. At the end of this period, a colourless solid separated out of the reaction mixture and was collected by filtration. The insoluble solid was washed with hexane (10 mL) and then dried. The crude product was recrystallized from ethanol solvent to obtain 5.

5a: mp: >220°C; IR (KBr) 3017–3165 cm$^{-1}$ (broad, medium, -NH-), 1661 cm$^{-1}$ (sharp, strong, -CO- of amide group), 1600 cm$^{-1}$ (sharp, strong, -CO-); $^1$H- NMR (DMSO-d$_6$, 400 MHz): 7.2–8.6 (m, 10H, Ar-H & C=CH), 11.1 (s, 1H, -NH, D$_2$O exchangeable), 12.6 (s, 1H, -NH, D$_2$O exchangeable); 13C-NMR (DMSO-d$_6$, 400 MHz): δ 92.8, 109.8, 112.9, 117.8, 118.4, 122.0, 123.6, 123.8, 127.1, 129.3, 132.1, 135.3, 136.1, 144.8, 162.0, 165.1; M$^+$+1 = 357.

5b: mp: >220°C; IR (KBr) 3012–3264 cm$^{-1}$ (broad, medium, -NH-), 1668 cm$^{-1}$ (sharp, strong, -CO- of amide group), 1605 cm$^{-1}$ (sharp, strong, -CO-); $^1$H- NMR (DMSO-d$_6$, 400 MHz): 7.4–8.6 (m, 9H, Ar-H & C=CH), 11.2 (s, 1H, -NH, D$_2$O exchangeable), 12.4 (s, 1H, -NH, D$_2$O exchangeable); 13C-NMR (DMSO-d$_6$, 400 MHz): δ 92.6, 108.3, 111.4, 115.3, 117.3, 122.3, 123.4, 123.9, 127.3, 130.3, 136.3, 138.3, 143.2, 161.4, 164.2; M$^+$+1 = 435.

5c: mp: >220°C; IR (KBr) 3016–3232 cm$^{-1}$ (broad, medium, -NH-), 1670 cm$^{-1}$ (sharp, strong, -CO- of amide group), 1610 cm$^{-1}$ (sharp, strong, -CO-); $^1$H- NMR (DMSO-d$_6$, 400 MHz): 7.1–8.6 (m, 9H, Ar-H & C=CH), 11.3 (s, 1H, -NH, D$_2$O exchangeable), 12.4 (s, 1H, -NH, D$_2$O exchangeable); 13C-NMR (DMSO-d$_6$, 400 MHz): δ 91.3, 108.3, 111.5, 115.4, 118.3, 121.4, 123.5, 123.7, 124.2, 129.5, 132.3, 134.3, 135.2, 141.5, 160.1, 164.2; M$^+$+1 = 402.

Preparation of 6 from 5 and alkylating agents
A mixture of 5 (10 mmol), alkylating agent (10 mmol) and triethanolamine (20 mL) was heated at 80°C for 90–100 min. At the end of this period, a colouress

| Entry | Starting material used | Alkylation agent | Product | Time (min) | Yield (%) |
|-------|------------------------|-----------------|---------|------------|-----------|
| 1     | 8                      | 10a (X = H, R = CH$_3$) | 6a      | 60         | 83        |
| 2     | 8                      | 10b (X = H, R = C$_2$H$_5$) | 6b      | 90         | 75        |
| 3     | 8                      | 10c (X = H, R = C$_4$H$_9$) | 6c      | 90         | 85        |
| 4     | 8                      | 10d (X = H, R = CH$_2$-Ph) | 6d      | 90         | 78        |
| 5     | 8                      | 10e (X = H, R = SO$_2$-Ph) | 6e      | 75         | 78        |
| 6     | 8                      | 10f (X = Br, R = CH$_3$) | 6f      | 90         | 75        |
| 7     | 8                      | 10g (X = Br, R = C$_2$H$_5$) | 6g      | 120        | 80        |
| 8     | 8                      | 10h (X = Br, R = C$_4$H$_9$) | 6h      | 120        | 85        |
| 9     | 8                      | 10i (X = Br, R = CH$_2$-Ph) | 6i      | 90         | 84        |
| 10    | 8                      | 10j (X = Br, R = SO$_2$-Ph) | 6j      | 120        | 83        |
| 11    | 8                      | 10k (X = NO$_2$, R = CH$_3$) | 6k      | 90         | 82        |
| 12    | 8                      | 10l (X = NO$_2$, R = C$_2$H$_5$) | 6l      | 120        | 80        |
| 13    | 8                      | 10m (X = NO$_2$, R = C$_4$H$_9$) | 6m      | 90         | 78        |
| 14    | 8                      | 10n (X = NO$_2$, R = CH$_2$-Ph) | 6n      | 90         | 85        |
| 15    | 8                      | 10o (X = NO$_2$, R = SO$_2$-Ph) | 6o      | 90         | 75        |

*Yields of crude products only.
solid separated out of the reaction mixture and was collected by filtration. The ininsoluble solid was washed with hexane (10 mL) and then dried. The crude product was recrystallized from ethanol solvent to obtain 6.

6a: mp: >220°C; IR (KBr): 3316–3374 cm⁻¹ (broad, medium, -NH-), 1658 cm⁻¹ (sharp, strong, -CO- of amide group), 1601 cm⁻¹ (sharp, strong, -CO-);

1H-NMR (DMSO-d₆, 400 MHz): 4.0 (s, 3H, CH₃), 7.3–8.6 (m, 10H, Ar-H & C=CH), 11.1 (s, 1H, -NH, D₂O exchangeable); 13C-NMR (DMSO-d₆, 400 MHz): δ 33.8, 92.5, 108.8, 111.4, 117.6, 118.5, 122.4, 123.6, 123.8, 127.6, 129.3, 135.2, 135.3, 136.8, 144.0, 162.0, 165.1; M⁺+1 = 371.

6b: mp: >220°C; IR (KBr): 3310–3390 cm⁻¹ (broad, medium, -NH-), 1650 cm⁻¹ (sharp, strong, -CO- of amide group), 1610 cm⁻¹ (sharp, strong, -CO-);

1H-NMR (DMSO-d₆, 400 MHz): 4.1 (m, 2H, CH₂), 2.2 (t, 3H, CH₃), 7.3–8.4 (m, 10H, Ar-H & C=CH), 11.1 (s, 1H, -NH, D₂O exchangeable); 13C-NMR (DMSO-d₆, 400 MHz): δ 23.0, 34.6, 90.3, 104.4, 110.3, 114.6, 115.6, 120.3, 122.4, 124.4, 125.2, 128.2, 134.5, 135.5, 136.7, 143.5, 161.3, 164.4; M⁺+1 = 385.

6c: mp: 210–212°C; IR (KBr): 3311–3383 cm⁻¹ (broad, medium, -NH-), 1654 cm⁻¹ (sharp, strong, -CO- of amide group), 1612 cm⁻¹ (sharp, strong, -CO-);

1H-NMR (DMSO-d₆, 400 MHz): 4.0 (t, 2H, CH₂), 2.0 (m, 2H, CH₃), 1.8 (m, 2H, CH₂), 1.2 (t, 3H, CH₃), 7.3–8.4 (m, 10H, Ar-H & C=CH), 11.1 (s, 1H, -NH, D₂O exchangeable); 13C-NMR (DMSO-d₆, 400 MHz): δ 21.0, 23.4, 24.8, 31.3, 90.2, 107.3, 111.3, 116.1, 118.3, 122.2, 123.4, 123.9, 127.4, 129.6, 130.1, 132.3, 134.2, 144.1, 161.2, 164.2; M⁺+1 = 413.

6d: mp: 220–222°C; IR (KBr): 3310–3370 cm⁻¹ (broad, medium, -NH-), 1653 cm⁻¹ (sharp, strong, -CO- of amide group), 1603 cm⁻¹ (sharp, strong, -CO-);

1H-NMR (DMSO-d₆, 400 MHz): 4.0 (t, 2H, CH₂), 7.4–8.6 (m, 15H, Ar-H & C=CH), 11.1 (s, 1H, -NH, D₂O exchangeable); 13C-NMR (DMSO-d₆, 400 MHz): δ 31.1, 91.1, 105.2, 110.1, 111.2, 112.4, 113.2, 115.5, 117.5, 118.3, 121.3, 122.5, 123.7, 125.3, 128.2, 134.3, 136.6, 136.8, 137.7, 144.2, 162.1, 164.2; M⁺+1 = 447.

6e: mp: >220°C; IR (KBr): 3290–3370 cm⁻¹ (broad, medium, -NH-), 1653 cm⁻¹ (sharp, strong, -CO- of amide group), 1602 cm⁻¹ (sharp, strong, -CO-);

1H-NMR (DMSO-d₆, 400 MHz): 7.4–8.6 (m, 15H, Ar-H & C=CH), 11.2 (s, 1H, -NH, D₂O exchangeable); 13C-NMR (DMSO-d₆, 400 MHz): δ 30.1, 92.2, 105.7, 109.1, 111.2, 111.3, 112.5, 114.6, 116.7, 117.7, 120.3, 121.5, 124.8, 124.9, 126.3, 130.4, 134.2, 135.7, 136.3, 140.2, 160.1, 164.0; M⁺+1 = 574.

6f: mp: >220°C; IR (KBr): 3313–3379 cm⁻¹ (broad, medium, -NH-), 1659 cm⁻¹ (sharp, strong, -CO- of amide group), 1600 cm⁻¹ (sharp, strong, -CO-);

1H-NMR (DMSO-d₆, 400 MHz): 7.2–8.9 (m, 9H, Ar-H & C=CH), 11.2 (s, 1H, -NH, D₂O exchangeable) 13C-NMR (DMSO-d₆, 400 MHz): δ 32.8, 91.5, 105.7, 110.3, 114.9, 118.4, 121.3, 122.4, 126.3, 127.5, 127.8, 134.1, 134.6, 135.9, 143.2, 162.0, 165.4; M⁺+1 = 416.
EtOH (20 mL) was stirred at RT for 40 min. A mixture of 4 (10 mmol), alkylating agent (10 mmol) and triethanolamine (20 mL) was heated at 80°C for 90–100 min. At the end of this period, a colourless solid separated out of the reaction mixture and was collected by filtration. The insoluble solid was washed with hexane (10 mL) and then dried. The crude product was recrystallized from ethanol solvent to obtain 6.

Preparation of 8 from 3
A mixture of 3 (10 mmol) and DMF-DMA (10 mmol) was stirred at RT for 10 min. At the end of this period, a colourless solid separated out of the reaction mixture and was collected by filtration. The insoluble solid was washed with hexane (10 mL) and then dried. The crude product was recrystallized from ethanol solvent to obtain 8.

Preparation of 6 from 8 and 10
A mixture of 8 (10 mmol), 10 (10 mmol) and AcOH (20 mL) was refluxed for 60–90 min. At the end of this period, a colourless solid separated out of the reaction mixture and was collected by filtration. The insoluble solid was washed with hexane (10 mL) and then dried. The crude product was recrystallized from ethanol solvent to obtain 6.

Preparation of 5 from 8 and 9
A mixture of 8 (10 mmol), 9 (10 mmol) and AcOH (20 mL) was refluxed for 60–90 min. At the end of this period, a colourless solid separated out of the reaction mixture and was collected by filtration. The insoluble solid was washed with hexane (10 mL) and then dried. The crude product was recrystallized from ethanol solvent to obtain 5.

Preparation of 6 from 5 and alkylating agents
A mixture of 5 (10 mmol), alkylating agent (10 mmol) and triethanolamine (20 mL) was heated at 80°C for 90–100 min. At the end of this period, a colourless solid separated out of the reaction mixture and was collected by filtration. The insoluble solid was washed with hexane (10 mL) and then dried. The crude product was recrystallized from ethanol solvent to obtain 6.
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Supplemental data

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