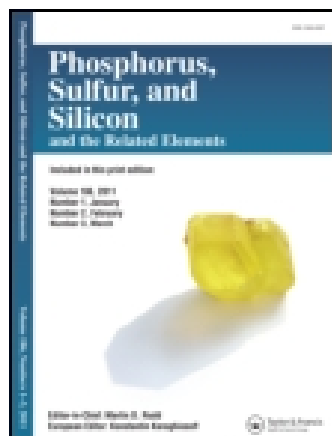


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### Synthesis of New Substituted N-Sulfonyl Pyrrolidine-2,5-Dione Using Dawson-Type Heteropolyacid as Catalyst

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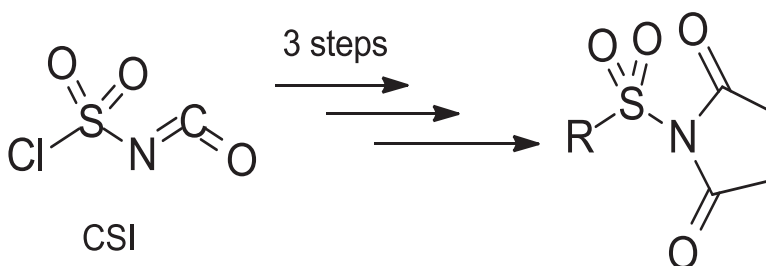


## SYNTHESIS OF NEW SUBSTITUTED *N*-SULFONYL PYRROLIDINE-2,5-DIONE USING DAWSON-TYPE HETEROPOLYACID AS CATALYST

Chafika Bougheloum, Robila Belghiche,  
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### GRAPHICAL ABSTRACT



**Abstract** The synthesis of new series of pyrrolidine-2,5-diones having sulfonamide moieties is described. These compounds are synthesized in good yield in three steps (carbamoylation-sulfamoylation, deprotection and condensation) using a catalytic amount of  $H_6P_2W_{18}O_{62}$  in acetonitrile under refluxing conditions.

**Keywords** Sulfonamide; Dawson heteropolyacid; catalyst; succinic anhydride; pyrrolidine-2; 5-diones

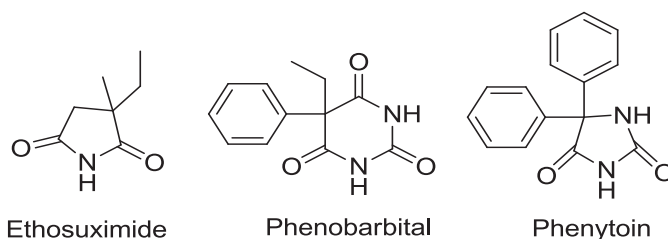
## INTRODUCTION

Heterocyclic compounds are important and valuable parts of biologically active molecules and natural products;<sup>1</sup> therefore, the design of new strategies to synthesize them is currently an important area of research. An interesting class of these compounds is pyrrolidine-2,5-diones, which are commonly referred to as succinimides; they are characterized by the presence of the fragment  $-(CO)NR(CO)-$  as belonging to the five-membered ring.<sup>2</sup>

These cyclic imides show great bioactive and pharmacological potential acting as enzyme inhibitors,<sup>3</sup> analgesics,<sup>4</sup> antimicrobial agents,<sup>5</sup> anxiolytics,<sup>6</sup> cytotoxic,<sup>7</sup> but mainly as anticonvulsants<sup>8</sup> (Figure 1).

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**Figure 1** Anticonvulsant drugs containing the fragment  $-(\text{CO})\text{NR}(\text{CO})-$ .

Previously, we reported the synthesis of the acyl sulfamides<sup>9</sup> via acylation of de-protected sulfamides with acetic anhydride. In this work, we describe the synthesis of pyrrolidine-2,5-diones having sulfonamide moieties using an acylating agent.

The sulfonamide group is considered as a pharmacophore, which is present in a number of biologically active molecules, particularly antimicrobial agents.<sup>10</sup>

It was shown that sulfonamide moieties can enhance largely the activity of antibacterial agents especially against both Gram-positive and Gram-negative bacteria.<sup>11</sup> In addition, the sulfonamide derivatives constitute an important class of drugs, with several types of pharmacological agents possessing antibacterial,<sup>12</sup> antitumor,<sup>13</sup> antiepileptic,<sup>14</sup> anticonvulsant,<sup>15</sup> or protease inhibitory activity<sup>16</sup> among others.

A number of synthetic methods have been developed in recent years to uncover a variety of new reagents for the synthesis of pyrrolidine-2,5-diones derivatives.<sup>17</sup> Recently, it has been reported that succinimides can also be synthesized by addition reactions of amines to olefinic bond of maleimides<sup>18</sup> in the presence of a catalyst.

However, these methods suffer from some disadvantages that involve long-reaction time, harsh reaction conditions, and unsatisfactory yields by using high temperatures and the hydrolysis reaction.<sup>8,17</sup> In addition, more than one step is involved in the synthesis of these compounds.

Therefore, the development of an efficient method for the synthesis of these compounds is an active ongoing research area and there is scope for further improvement toward milder reaction conditions and higher yields.

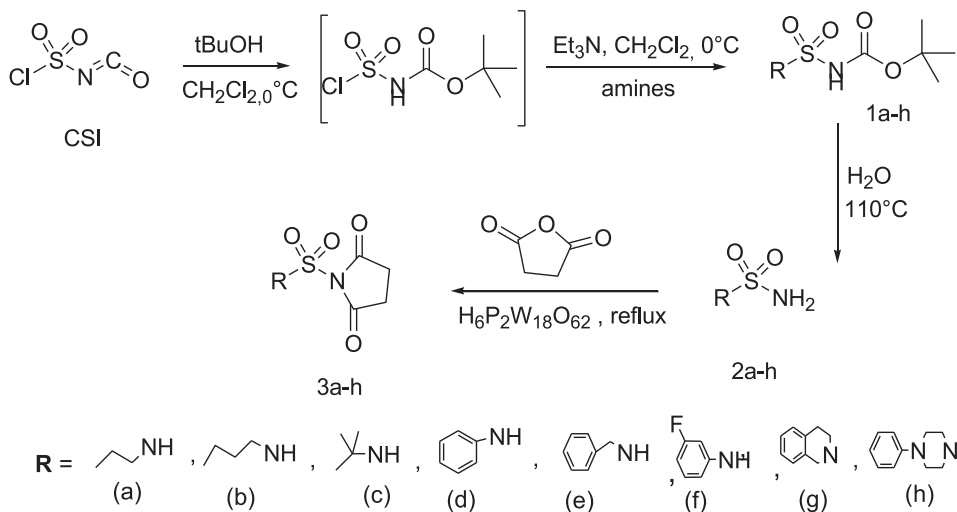
Over the last few years, there has been a considerable growth in interest in the use of heteropolyacids, HPAs, in organic synthesis because of their ease of handling, enhance reaction rates, low cost, simple work-up, and recyclability of the catalyst.<sup>19–23</sup>

In continuation of our investigation on the use of heteropolyacids as catalyst for chemical synthesis,<sup>9</sup> we wish to report a simple, convenient, and efficient method for the preparation of *N*-sulfonyl pyrrolidine-2,5-diones derivatives from sulfamides and succinic anhydride in the presence of catalytic amounts of Dawson type heteropolyacid  $\text{H}_6\text{P}_2\text{W}_{18}\text{O}_{62}$ , as an eco-friendly catalyst.

To the best of our knowledge, no *N*-sulfonyl pyrrolidine-2,5-diones derivatives have been reported to date (Scheme 1).

## RESULTS AND DISCUSSION

In our previous works, we have established that chlorosulfonyl isocyanate (CSI) is a suitable reagent allowing the introduction a sulfonamide moiety in biomolecules.<sup>24</sup> CSI is also the reagent of choice for the preparation of sulfonyl pyrrolidine-2,5-diones derivatives.



In this case, CSI contains the required sulfonyl group and the nitrogen, which is necessary for the formation of pyrrolidine-2,5-diones.

The synthetic pathway followed for the preparation of the title compounds was accomplished by a three-steps sequence as shown in Scheme 1. First, the alcohol, *t*-butanol, reacted smoothly with chlorosulfonyl isocyanate in the presence of dichloromethane to easily form the desired carbamate. In the second step, condensation of the carbamate with commercially available corresponding amines (propylamine, butylamine, *tert*-butylamine, aniline, benzylamine, 3-fluoroaniline, 1,2,3,4-tetrahydroisoquinoline and 1-phenyl piperazine) in the presence of triethylamine at 0°C afforded substituted sulfamides (1a–h) in good yields. These products were purified by chromatography on silica gel (eluted with DCM/MeOH: 9.1).

In the second step (Scheme 1), the deprotection of 1a–h in water with stirring at reflux temperature provided deprotected sulfamides (2a–h) in 80% yield.<sup>25</sup>

In the last stage of the synthesis, compounds (2a–h) were subjected to the condensation reaction in an acidic medium under solvent reflux. The condensation was attempted with a catalytic amount of Dawson-type heteropolyacid which showed its greater reactivity in the acylation of sulfamide,<sup>9</sup> yielding *N*-sulfonyl pyrrolidine-2,5-diones derivatives (3a–h).

Identification of all isolated products (1a–h), (2a–h), and (3a–h) was accomplished by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopies and mass spectrometry.

Initially, in order to find the optimal conditions, the reaction of 3,4-Dihydroisoquinoline-2(1H)-sulfonamide (2 g) (1 mmol) with succinic anhydride (2 mmol) in the presence of various amounts of H<sub>6</sub>P<sub>2</sub>W<sub>18</sub>O<sub>62</sub> in various solvents were used as a model reaction. The best result has been obtained at 2 mmol% of catalyst in acetonitrile (Entry 5, Table 1). In order to show the merit of the presented protocol, the model reaction between 3,4-Dihydroisoquinoline-2(1H)-sulfonamide (2 g) and succinic anhydride was described, and different catalysts such as H<sub>6</sub>P<sub>2</sub>W<sub>12</sub>Mo<sub>6</sub>O<sub>62</sub>, H<sub>3</sub>PW<sub>12</sub>O<sub>40</sub>, H<sub>2</sub>SO<sub>4</sub>, montmorillonite K10 were subjected to the reaction (Table 1).

It should be noted that a blank reaction without any catalyst gave no product even after 1 h under identical conditions (Entry 13, Table 1). It should be noted that, this method is

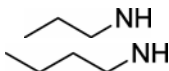
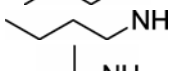
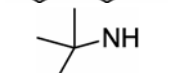
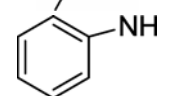
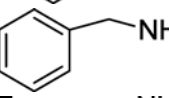
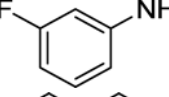
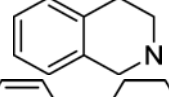
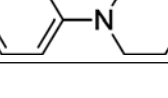
**Table 1** Synthesis of *N*-sulfonyl pyrrolidine-2,5-diones derivatives using various conditions

Entry	Solvent	Catalyst (mmol%)	Time (min)/ Conversion (%) <sup>a</sup>
1	CH <sub>2</sub> Cl <sub>2</sub>	H <sub>6</sub> P <sub>2</sub> W <sub>18</sub> O <sub>62</sub> (2)	60/58
2	CHCl <sub>3</sub>	H <sub>6</sub> P <sub>2</sub> W <sub>18</sub> O <sub>62</sub> (2)	60/62
3	THF	H <sub>6</sub> P <sub>2</sub> W <sub>18</sub> O <sub>62</sub> (2)	60/67
4	Toluene	H <sub>6</sub> P <sub>2</sub> W <sub>18</sub> O <sub>62</sub> (2)	60/75
5	CH <sub>3</sub> CN	H <sub>6</sub> P <sub>2</sub> W <sub>18</sub> O <sub>62</sub> (2)	60/90
6	CH <sub>3</sub> CN	H <sub>6</sub> P <sub>2</sub> W <sub>18</sub> O <sub>62</sub> (1.5)	60/85
7	CH <sub>3</sub> CN	H <sub>6</sub> P <sub>2</sub> W <sub>18</sub> O <sub>62</sub> (1)	60/73
8	CH <sub>3</sub> CN	H <sub>6</sub> P <sub>2</sub> W <sub>18</sub> O <sub>62</sub> (2.5)	60/90
9	CH <sub>3</sub> CN	H <sub>6</sub> P <sub>2</sub> W <sub>12</sub> Mo <sub>6</sub> O <sub>62</sub> (2)	60/84
10	CH <sub>3</sub> CN	H <sub>3</sub> PW <sub>12</sub> O <sub>40</sub> (2)	60/45
11	CH <sub>3</sub> CN	H <sub>2</sub> SO <sub>4</sub> (2)	60/30
12	CH <sub>3</sub> CN	K10(2)	60/15
13	CH <sub>3</sub> CN	None	60/00

<sup>a</sup>The conversion was determined by <sup>1</sup>H NMR analysis of the crude product.

effective for the preparation of *N*-sulfonyl pyrrolidine-2,5-dione derivatives from reaction of deprotected sulfamides with succinic anhydride. The optimized methodology was applied to the synthesis of some derivatives of *N*-sulfonyl pyrrolidine-2,5-diones. The results are summarized in Table 2. In all cases, good yields of products were obtained.

**Table 2** H<sub>6</sub>P<sub>2</sub>W<sub>18</sub>O<sub>62</sub> catalyzed synthesis of *N*-sulfonyl pyrrolidine-2,5-dione derivatives in acetonitrile under refluxing conditions

Entry	<i>R</i>	Product	Time(min)/Yield(%)
1		3a	60/80
2		3b	60/82
3		3c	60/85
4		3d	60/80
5		3e	60/83
6		3f	60/81
7		3g	60/84
8		3h	60/83

## CONCLUSION

In summary, we have developed an alternative and simple procedure for the synthesis of *N*-sulfonyl pyrrolidine-2,5-diones derivatives from sulfamides and succinic anhydride using  $\text{H}_6\text{P}_2\text{W}_{18}\text{O}_{62}$ , as an eco-friendly, inexpensive, and efficient catalyst in various conditions.

The advantages of this catalytic system is mild reaction conditions, short-reaction times, high product yields, easy preparation of the catalysts, nontoxicity of the catalysts, simple and clean work-up of the desired products.

## EXPERIMENTAL

All the chemicals were commercially available and used as received.

$\text{H}_6\text{P}_2\text{W}_{18}\text{O}_{62}$  was prepared according to the literature.<sup>26</sup> Melting points were determined in open capillary tubes on Buchi B-540. Proton nuclear magnetic resonance was determined with a 400-MHz Bruker spectrometer using  $\text{CDCl}_3$  and  $\text{DMSO-d}_6$  as solvent and TMS as an internal standard. Chemical shifts are reported in  $\delta$  units (ppm). All coupling constants *J* are reported in Hertz. Multiplicity is indicated as s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet), and combination of these signals. The mass spectra were recorded on a DSQ Thermoelectron apparatus (70 eV) by chemical ionization (gaseous ammonia) by direct introduction. Elemental analysis was performed with a Perkin-Elmer 2400 C, H, N analyzer and determined values were within the acceptable limits of the calculated values. Figures S1 to S16 (Supplemental Materials) are sample  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, and mass spectra for selected compounds.

### General Procedure For The Synthesis of *N*-sulfonyl Pyrrolidine-2,5-Diones (3a–h);

Under nitrogen atmosphere, a mixture of sulfamide (1 mmol), succinic anhydride (2 mmol), and  $\text{H}_6\text{P}_2\text{W}_{18}\text{O}_{62}$  catalyst (2 mmol%) in acetonitrile (2 mL), was stirred at reflux. Reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated, diluted with water (10 mL) to solubilize the catalyst, and extracted with EtOAc (3  $\times$  15 mL), the combined organic layers were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , then the solvent was evaporated in vacuum, and the crude compound was purified by flash chromatography (Merck silica gel 60 H,  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 9:1) to afford the corresponding sulfonyl pyrrolidine-2,5-dione derivatives.

### *N*-(propyl)-2,5-dioxopyrrolidine-1-sulfonamide (3a)

Yield: 80%, mp 134°C, Rf = 0.82 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 9/1),  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ,  $\delta$  ppm): 1.1 (t, *J* = 5.02 Hz, 3H,  $\text{CH}_3$ ), 1.69 (m, 2H,  $\text{CH}_2$ ), 2.67 (s, 4H,  $2\text{CH}_2\text{-CO}$ ); 3.32 (m, 2H,  $\text{CH}_2$ ), 5.3 (t, *J* = 5.4 Hz, 1H, NH).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ,  $\delta$  ppm): 11.3, 22.2, 28.1, 42.7, 177.6. MS( $\text{ESI}^+$ 70 eV) : 58.04 (14%), 238 ( $[\text{M}+\text{NH}_4]^+$ , 100%).

Elemental anal. (%), calculated: C, 38.18; H, 5.45; N, 12.72; found: C, 38.23; H, 5.49; N, 12.68.

**N-(butyl)-2,5-dioxopyrrolidine-1-sulfonamide (3b)**

Yield: 82%, mp 136°C, Rf = 0.80(CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 9/1), <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ ppm): 0.89 (t, *J* = 5.02 Hz, 3H, CH<sub>3</sub>), 1.37 (m, 2H, CH<sub>2</sub>), 1.57 (m, 2H, CH<sub>2</sub>), 2.70 (s, 4H, 2CH<sub>2</sub>-CO), 3.07 (m, 2H, CH<sub>2</sub>-N). <sup>13</sup>C NMR (CDCl<sub>3</sub>, δ ppm): 13.5, 19.8, 28.8, 30.9, 43.5, 179.3. MS (ESI<sup>+</sup> 70 eV *m/z*): 72.09 (10%), 235(35%), 252.10 ([M+NH<sub>4</sub>]<sup>+</sup>, 100%). Elemental anal. (%), calculated: C, 41.02; H, 5.98; N, 11.96; found: C, 41.12; H, 5.88; N, 11.87.

**N-(tert-butyl)-5-dioxopyrrolidine-1-sulfonamide (3c)**

Yield: 85%, mp 138°C, Rf = 0.83(CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 9/1), <sup>1</sup>H NMR(CDCl<sub>3</sub>, δ ppm): 1.35(s, 9H, 3(CH<sub>3</sub>)); 2.65(s, 4H, 2CH<sub>2</sub>CO). <sup>13</sup>C NMR(CDCl<sub>3</sub>, δ ppm): 28.3, 29.6; 44.9, 176.6. Ms(ESI<sup>+</sup> 70 eV *m/z*): 72.05(10%), 252.09 ([M+NH<sub>4</sub>]<sup>+</sup>, 100%).

Elemental anal. (%), calculated: C, 41.02; H, 5.98; N, 11.96; found: C, 41.08; H, 5.99; N, 11.99.

**N-(phenyl)-2,5-dioxopyrrolidine-sulfonamide (3d):**

Yield: 80%, mp 149°C, Rf = 0.78(CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 9/1), <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ ppm): 2.77(s, 4H, 2CH<sub>2</sub>-CO), 6.86(m, 3H, Ar-H), 7.22(m, 2H, Ar-H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, δ ppm): 28.6, 117.9; 121.1, 129.5, 139.6, 175.8. MS (ESI<sup>+</sup> 70 eV *m/z*): 255.13 (15%), 272.14([M+NH<sub>4</sub>]<sup>+</sup>, 85%).

Elemental anal. (%), calculated: C, 47.24; H, 3.94; N, 11.02; found: C, 47.34; H, 3.87; N, 11.09.

**N-benzyl-2,5-dioxopyrrolidine-1-sulfonamide (3e):**

Yield: 83%, mp 141°C, Rf = 0.81(CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 9/1), <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ ppm): 2.10(s, 4H, 2CH<sub>2</sub>CO), 4.10(d, *J* = 4.02 Hz, 2H, CH<sub>2</sub>-Ph), 7.26(m, 5H, H-Ar). <sup>13</sup>C NMR (CDCl<sub>3</sub>, δ ppm): 28.4, 44.5, 128.2, 128.7, 129.4, 138.8, 172.4. MS (ESI<sup>+</sup> 70 eV *m/z*): 105.98 (8%), 296.13([M+1]<sup>+</sup>, 15%), 286.16 ([M+NH<sub>4</sub>]<sup>+</sup>, 100%).

Elemental anal. (%), calculated: C, 49.25; H, 4.47; N, 10.45; found: C, 49.34; H, 4.39; N, 10.49.

**N-(3-fluorophenyl)-2,5-dioxopyrrolidine-1-sulfonamide (3f):**

Yield: 81%, mp 158°C, Rf = 0.77(CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 9/1), <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ ppm): 2.94(s, 4H, 2CH<sub>2</sub>CO), 6.94(m, 1H, H-Ar), 7.26(m, 1H, H-Ar), 7.46(m, 1H, H-Ar), 7.66(m, 1H, H-Ar). <sup>13</sup>C NMR (CDCl<sub>3</sub>, δ ppm): 28.6, 105.6, 110.1, 114.6, 130.7, 139.4, 163.9, 173.3. MS (ESI<sup>+</sup> 70 eV *m/z*): 111.04 (10%), 175.04 (10%), 290.10 ([M+NH<sub>4</sub>]<sup>+</sup>, 100%).

Elemental anal. (%), calculated: C, 44.12; H, 3.31; N, 10.29; found: C, 44.04; H, 3.38; N, 10.19.

**1-(3,4-Dihydroisoquinolin-2(1H)-yl) Sulfonyl Pyrrolidine-2,5-dione (3g):**

Yield: 84%, mp 132°C, Rf = 0.82(CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 9/1), <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ ppm): 2.67 (s, 4H, 2CH<sub>2</sub>-CO), 2.91(t, 2H, *J* = 5.8 Hz, CH<sub>2</sub>-ph), 3.73(t, 2H, *J* = 5.7 Hz, CH<sub>2</sub>N), 4.59(s, 2H, CH<sub>2</sub>N), 7.02(m, 1H, Ar-H), 7.08(m, 1H, Ar-H), 7.14(m, 2H, Ar-H). <sup>13</sup>C NMR

(CDCl<sub>3</sub>,  $\delta$  ppm): 28.5, 28.5, 44.6, 47.4, 126.3, 126.6, 127.2, 128.9, 131.1, 133.2, 172.5. MS (ESI<sup>+</sup> 70 eV  $m/z$ ): 102.00(17%), 132.04(31%), 156.08(17%), 219.99(27%), 229.99(43%), 295.04([M+H]<sup>+</sup>, 10%), 312.05 ([M+NH<sub>4</sub>]<sup>+</sup>, 100%).

Elemental anal. (%), calculated: C, 53.06; H, 4.76; N, 9.52; found: C, 53.12; H, 4.81; N, 9.63.

### 1-((4-Phenylpiperazine-1yl)sulfonyl)pyrrolidine-2,5-dione (3h):

Yield: 83%, mp 152°C, R<sub>f</sub> = 0.78(CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 9/1), <sup>1</sup>H NMR (CDCl<sub>3</sub>,  $\delta$  ppm): 2.77(s, 4H, 2CH<sub>2</sub>-CO), 3.21(t, 4H, CH<sub>2</sub>-N), 3.56(t, 4H, CH<sub>2</sub>-N), 6.86(m, 3H, Ar-H), 7.22(m, 2H, Ar-H). <sup>13</sup>C NMR (CDCl<sub>3</sub>,  $\delta$  ppm): 28.6, 46.4, 49.1, 117.1, 121.1, 129.4, 150.6, 172.6. MS (ESI<sup>+</sup> 70 eV  $m/z$ ): 161.20 (6%), 216.00 (6%), 241.99(7%), 324.02([M+H]<sup>+</sup>, 100%).

Elemental anal. (%), calculated: C, 52.01; H, 5.26; N, 13.00; found: C, 52.11; H, 5.33; N, 13.09.

## SUPPLEMENTAL MATERIAL

Supplementary data for the article (Full experimental detail for the first two steps and supplemental data of new compounds (3a–h).) can be accessed on the publisher's website at <http://doi.dx.org/10.1080/10426507.2014.947413>.

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