

Utility of Sulphones in Heterocyclic Synthesis: Synthesis of Some Pyridine, Chromene and Thiophene Derivatives

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Abstract: Phenylsulfonylacetonitrile (**1**) when reacted with α,β -unsaturated nitriles (**2a,b**) and/or 2-hydroxynaphthaldehyde yields pyridine derivatives (**3a,b**) and / or the imino-chromene derivative (**4**) respectively. The behavior of (**1**) towards some α -halogenated compounds has been investigated.

Keywords: Phenylsulfonylacetonitrile, pyridine derivatives, chromene derivatives, thiophene derivatives.

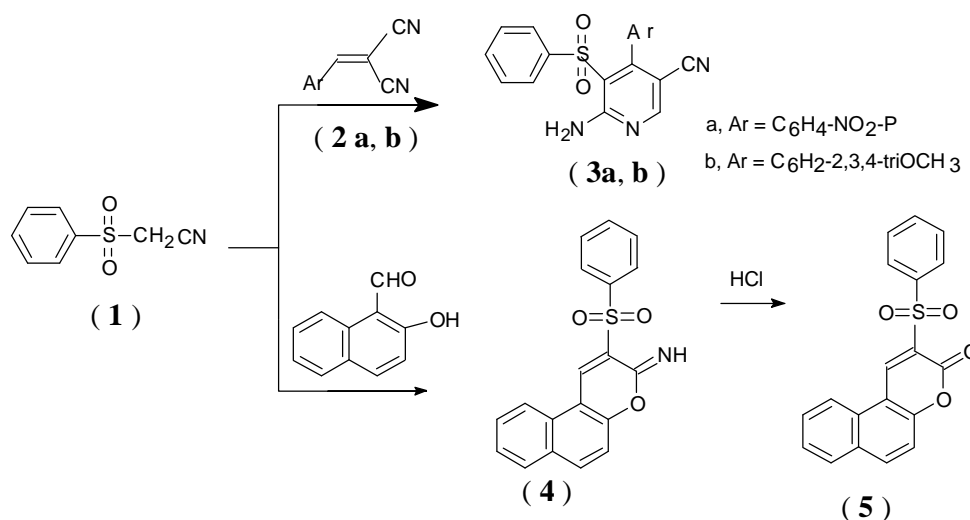
Introduction

This work is the continuation of a program with the aim to develop new simple methods for the synthesis of functionally substituted heterocycles with anticipated biological activity. We have recently extended it to include the investigation of the pharmacological aspects of the newly synthesized heterocycles based on the finding that some heterocycles can achieve activity in both the pharmacological and pesticidal areas, e.g. thiabendazole, the well known human and veterinary anthelmintic, is also used as a fungicide [1,2].

Results and Discussion

Pyridines and chromene derivatives have recently received considerable attention due to their synthetic and pharmaceutical importance and different approaches for their synthesis have been developed [3,5a-c]. In the last few years the authors have been exploring the synthetic potential, scope, and limitations of activated nitriles in heterocyclic synthesis [6-8]. Several new approaches for the synthesis of five and six membered rings and their fused heterocyclic derivatives have been developed during this work [9,10]. In the present work we explore the synthetic potential of phenylsulfonyl-acetonitrile (**1**) to form polysubstituted pyridines and chromene heterocycles via the reaction of **1** with α,β -unsaturated nitriles (**2a,b**) and 2-hydroxynaphthaldehyde respectively.

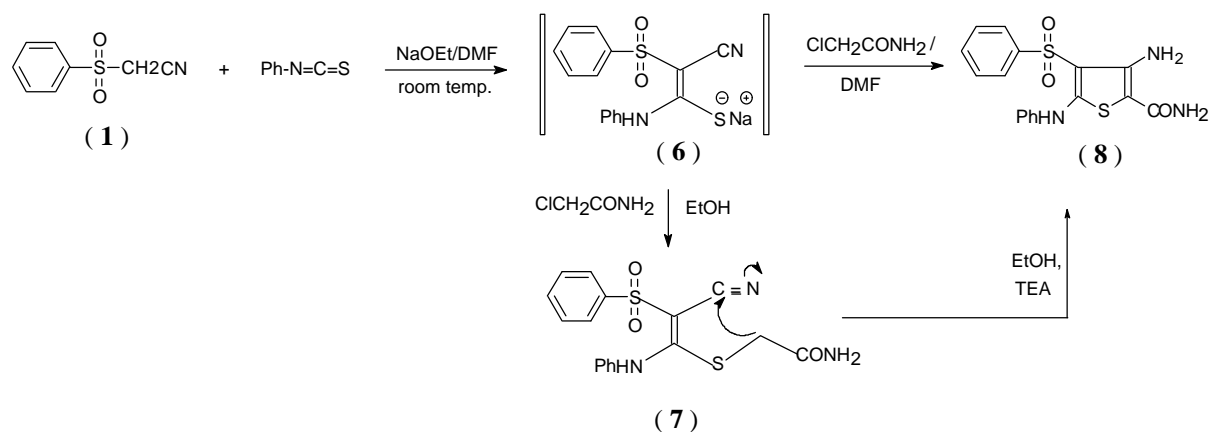
Thus, compound **1** reacts under TEA catalysis with α,β -unsaturated nitriles (**2a,b**) in refluxing ethanol to afford 2-amino-3-phenylsulfonyl-4-aryl-5-carbonitrile pyridines **3a,b** as coloured solid products [11]. The IR spectrum of these products showed in each case, absorption bands at ν 3350-3400, 2220, and 1610 cm^{-1} corresponding to NH_2 , CN, and C=N groups respectively. Structures **3a,b** were assigned to these products on the basis of the spectral as well as analytical data (cf. Table 1). The $^1\text{H-NMR}$ spectrum of **3a** revealed a broad singlet at δ 6.5 ppm assigned to the amine protons and a multiplet at δ 7.8- 8.4 ppm assigned to the pyridine-2H and aromatic protons.



Scheme 1.

Compound (**1**) reacts with 2-hydroxy naphthaldehyde in refluxing ethanol in the presence of TEA to give 2-imino-3-phenylsulfonyl-benzo[f]chromene (**4**) in high yield. Mass spectral measurements and analytical data are in complete agreement with structure 4 (M^+ 335). Moreover, the resulting coumarin derivatives have latent functional substituents, which have the potential for further chemical transformations giving new routes for the preparation of substituted coumarin derivatives with possible biological activity. 3-Phenylsulfonyl-2H-benzo[f]-2-chromenone (**5**) was synthesized via hydrolysis of (**4**) in a mixture of conc. hydrochloric acid and ethanol. The mass spectrum of (**5**) showed the expected molecular formula C₁₉H₁₂O₄S (M^+ 336).

Previously, we investigated the reaction of phenyl isothiocyanate with active methylene compounds in alkaline medium, which has proved to be a convenient route for the synthesis of thiazole, pyrazole, oxazine and pyrimidine ring systems [7]. Now, we have extended our synthetic program to the synthesis of otherwise inaccessible heterocyclic ring systems, utilizing phenyl isothiocyanate as a key starting material. It is known that a great variety of reactants bearing the $N=C=S$ fragment undergo cyclization on reaction with α -halocarbonyl compounds to afford thiazoles, 2,3-dihydrothiazoles and thiazolidines [12], which have been shown to exhibit local anaesthetic [13], antiprotozoal [14] and fungicidal properties [15]. In this paper, we describe a generally applicable extension of this synthetic approach, first reported by Hantzsch and Weber [16]. Thus, the base-prompted reaction of the acidic methylene compound **1** with phenyl isothiocyanate in dry DMF at room temperature yields the non-isolable intermediate **6**. Treatment of **6** with α -chloroacetamide in boiling DMF yielded a product (**8**), which analyzed correctly for $C_{17}H_{15}N_3O_3S_2$. The structure **8** was inferred from its spectral data. Thus, the IR spectrum showed absorption bands at ν 3450, 3150, 1661, 1550, 1270 and 1180 cm^{-1} corresponding to NH_2 , NH , $C=O$, Ph and SO_2 functions and the absence of a CN stretching band. Its 1H -NMR spectrum showed a broad singlet at δ 5.5- 6.2 ppm (4H), two multiplet signals integrated for (10 H) centered at 7.4 and 8.0 (aromatic protons) and a singlet (1H) at 8.6. On shaking the compound with D_2O , the broad band signals at δ 5.5- 6.2 ppm and 8.6 disappeared. Based on the foregoing data, structure **8** was assigned to this product. The structure of **8** was further confirmed by its alternative synthesis. Thus, it was found that, treatment of **6** with α -chloroacetamide in refluxing ethanol produced the acyclic intermediate **7**. Structure **7** was suggested for the reaction product on the basis of both elemental and spectral analysis. The IR spectrum showed the presence of a cyano absorption band at ν 2220 cm^{-1} , NH_2 , NH and $C=O$ (amidic) functions at ν 3340, 3150 and 1680 cm^{-1} respectively. Refluxing **7** in ethanol with a few drops of TEA led to the formation of a product identical in all respects (m.p., mixed m.p., IR, 1H -NMR) to **8**.

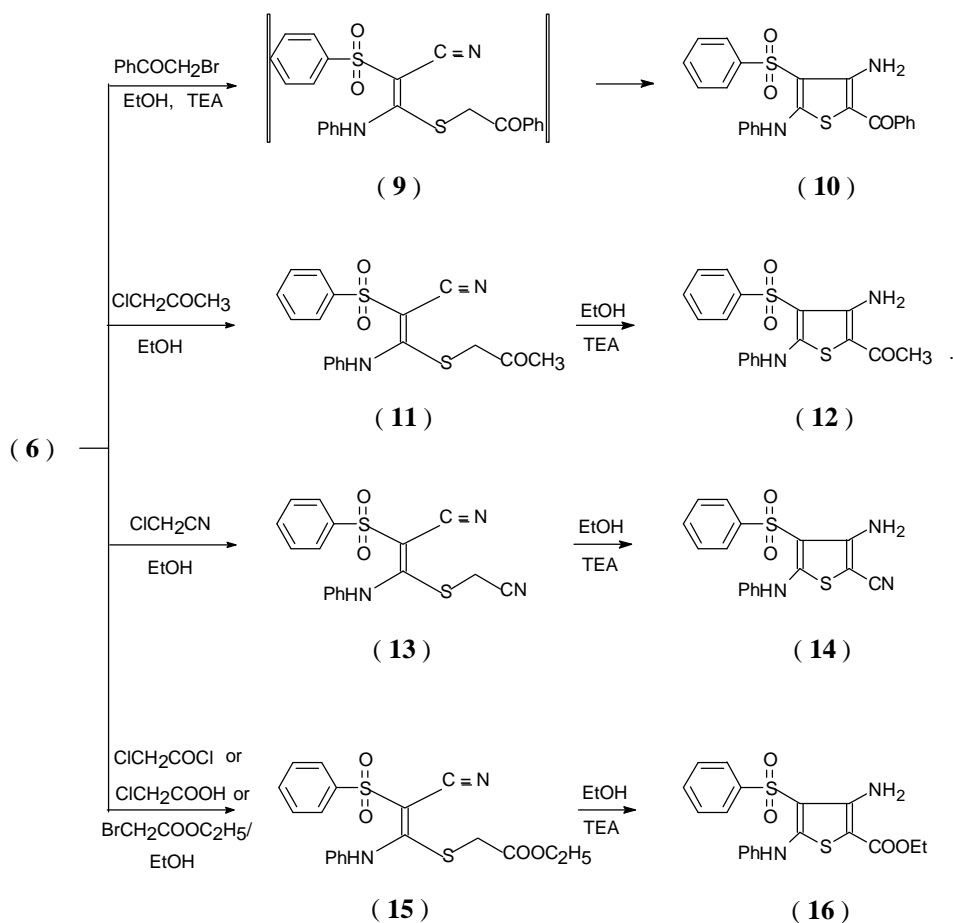


Scheme 2.

The intermediate **6** also undergoes in-situ cyclization upon the reaction with equimolar amounts of phenacyl bromide in boiling ethanol and a catalytic amount of TEA, giving a yellow colored product (**10**). The phenylsulfonyl thiophene structure **10** was suggested for this product on the basis of analytical and spectral data (cf. Table 1). The mass spectrum of **10** showed molecular formula $C_{23}H_{18}N_2O_3S_2$

($M^+ = 434$). The reaction may occur through the non-isolable intermediacy of a cyclic derivative (**9**). Attempts to isolate **9** by refluxing phenacyl bromide with the intermediate **6** in ethanol were unsuccessful. Compound **10** is assumed to be formed via the acyclic intermediate **9**.

Compound **6** reacted readily with chloroacetone in boiling ethanol to afford the acyclic intermediate **11** by NaCl elimination. Refluxing **11** in ethanol with a catalytic amount of TEA, gave the thiophene derivative **12** whose structure was confirmed by elementary analysis and spectral data. (cf. Table 1). The structure of **12** was further confirmed by its alternative synthesis. Thus, refluxing **6** with chloroacetone in DMF affords the thiophene derivative **12** in reasonably good yield. Similarly, when the intermediate **6** is treated with chloroacetonitrile in refluxing ethanol the corresponding acyclic intermediate **13** is exclusively isolated in good yield. The structure of **13** has been confirmed on the basis of elemental and spectral data. e.g. the IR spectrum exhibits bands at ν 3200 (NH), 2220, 2195 cm^{-1} (two cyano). Its $^1\text{H-NMR}$ spectrum reveals a CH_2 signal at δ 3.23 ppm. Furthermore, heating of the intermediate **13** in ethanol containing a catalytic amount of TEA affords the thiophene derivative **14**. The thiophene structure **14** was established based on its IR spectrum which showed bands related to NH_2 , NH and CN functions. Its $^1\text{H-NMR}$ spectrum reveals a multiplet at (δ ppm) 7.31-7.56 (10 H, aromatic), broad signals at δ 6.5 (2H, NH_2) and δ 8.7 ppm (1H, NH). On the other hand, it has been found that it is directly formed by refluxing **6** and chloroacetonitrile in DMF.



Scheme 3.

When **6** was treated with an equimolar amount of chloroacetyl chloride or with chloroacetic acid in boiling ethanol, a product that analyzed for $C_{19}H_{18}N_2O_4S_2$ was isolated in each case in good yield. The acyclic structure **15** was established based on its IR spectrum that showed bands related to NH, CN and CO functions. Its 1H -NMR spectrum reveals a multiplet at (δ ppm) 7.5- 8.56 (10 H, aromatic), a triplet signal at δ 1.3 (3H, CH_3), singlet at δ 3.7 (2H), quartet at δ 4.3 (2H, CH_2) and a D_2O exchangeable NH at 8.91 ppm. Alternatively, treatment of **6** with ethyl bromoacetate in refluxing ethanol gives a single product, which is identical in all respects to **15** (m.p., mixed m.p. and IR spectrum). The mass spectrum of **15** showed a molecular formula $C_{19}H_{18}N_2O_4S_2$ ($M^+ = 402$). Refluxing of **15** in ethanol with a catalytic amount of TEA afforded the corresponding thiophene derivative **16** [16] (cf. Table 1).

Conclusion

We report a facile route for the formation of pyridines, chromenes and thiophene derivatives based on sulfones.

Experimental

General

All melting points are uncorrected. FTIR spectra (KBr disk) were recorded on a Nicolet Magna-IR model 550 spectrophotometer, 1H NMR spectra in $CDCl_3$ were determined on a Bruker WPSY 200 MHz spectrometer with TMS as internal standard, and the chemical shifts are in δ ppm. Mass spectra were recorded at 70 eV with a Varian MAT 311

Synthesis of pyridine derivatives (**3a,b**). General procedure

A mixture of phenylsulfonylacetonitrile (**1**) (0.01 mol), α,β -unsaturated nitriles **2a,b** (0.01 mol) and catalytic amounts of TEA in ethanol (15 mL) were refluxed for 6 h. The solid product obtained after cooling was filtered off and recrystallized from ethanol to give the pyridine derivatives **3a,b** (cf. Table 1).

Synthesis of 2-imino-3-phenylsulfonyl-2H-benzof[*f*]chromene (**4**)

A mixture of phenylsulfonylacetonitrile (**1**) (0.01 mol), 2-hydroxy-1-naphthaldehyde (0.01 mol) and a catalytic amount of TEA in ethanol (15 mL) was refluxed for 2 h. The solid product iminochromene **4** obtained after cooling was recrystallized from ethanol. (cf. Table 1).

Synthesis of 3-phenylsulfonyl-2H-benzo[f]-2-chromenone (5)

3-Phenylsulfonyliminochromene (**4**) (0.01 mol) was heated in a mixture of conc. HCl and ethanol (1:1, 20 mL) for 15 min. The reaction mixture was left to stand at room temperature overnight, and the solid product was filtered and recrystallized from ethanol to give (**5**).

Preparation of compound (6)

To a stirred suspension of sodium ethoxide (0.23 g, from 0.01 mol sodium and 10 mL ethanol) in DMF (20 mL), phenylsulfonyl acetonitrile (0.01 mol) was added. To the resulting solution the phenyl isothiocyanate (0.01 mol) was added and the reaction mixture stirred for 24 h. at room temperature.

Synthesis of the acyclic intermediates 7, 11, 13 and 15. General procedure

Equimolecular quantities of **6** in ethanol and a α -chloroacetamide and/or chloroacetone and/or chloroacetonitrile and/or ethyl bromoacetate were stirred for 6 hr. at room temperature, then left to stand at the same temperature for 24 h. The reaction mixture was washed with water, dried and crystallized from ethanol to give **7**, **11**, **13** and **15** respectively (cf. Table 1).

Synthesis of thiophene derivatives (10)

A mixture of equimolecular amounts of **6** and phenacyl bromide (0.01 mol) was refluxed in ethanol (20 mL) containing a catalytic amount of TEA for 6 h. The reaction mixture was cooled, filtered and recrystallized from ethanol to give **10** (cf. Table 1).

Synthesis of thiophene derivatives (8, 12, 14 and 16)

Method A

A mixture of equimolecular amounts of **6**, and α -halo compounds (0.01 mol) was refluxed in DMF (20 mL) for 6 h. The reaction mixture was cooled, filtered and recrystallized from ethanol to give the corresponding thiophene derivatives. (cf. Table 1).

Method B

Refluxing the acyclic intermediate (**7**, **11**, **13** and/or **15**) in ethanol (20 mL) containing a catalytic amount of TEA for 3 h. afforded the corresponding substituted thiophene derivatives **8**, **12**, **14** and **16** respectively.

Table 1. Characterization of the newly prepared compounds.

No.	mp° C	Yld %	Mol. formula	Analysis Calcd. (Found %)			Characterization
				C	H	N	
3a	180	78	C ₁₈ H ₁₂ N ₄ O ₄ S (380.38)	56.71 (56.84)	3.14 (3.15)	14.71 (14.73)	IR: 3350- 3450 (NH ₂), 2220 (CN), 1610cm ⁻¹ (C=N); ¹ H-NMR (CDCl ₃) δ 6.5 (s, 2H, NH ₂ exchangeable with D ₂ O), 7.8-8.4 (m, 9H, Ar-H), 8.5 (s, 1H, o-Py-H); MS: (m/z) 380 M ⁺ .
3b	125	83	C ₂₁ H ₁₉ N ₃ O ₅ S (425.47)	59.10 (59.29)	4.43 (4.47)	9.87 (9.88)	IR: 3350- 3450 (NH ₂), 2220 (CN), 1610cm ⁻¹ (C=N); ¹ H-NMR (CDCl ₃) δ 3.8 (s, 3H, OCH ₃), 3.9 (s, 3H, OCH ₃), 4.0 (s, 3H, OCH ₃), 7.1 (d, 2H, NH ₂ exchangeable with D ₂ O), 7.7-8.0 (m, 6H, Ar-H), 8.5 (s, 1H, o-Py-H); MS: (m/z) 425 M ⁺ .
4	225	90	C ₁₉ H ₁₃ NO ₃ S (335.38)	68.00 (68.05)	3.84 (3.88)	4.15 (4.17)	IR: 3150 (NH), 1650 (C=N), 1561cm ⁻¹ (Ph); ¹ H-NMR (CDCl ₃) δ 7.3- 8.5 (m, 11H, Ar-H), 8.8 (s, 1H, NH exchangeable with D ₂ O), 9.2 (s, 1H, C ₄ -H); MS: (m/z) 335 M ⁺ .
5	267	98	C ₁₉ H ₁₂ O ₄ S (336.37)	67.69 (67.85)	3.56 (3.57)		IR: 1700 (γ-Lactone), 1555cm ⁻¹ (Ph); ¹ H-NMR (CDCl ₃) δ 7.55- 8.25 (m, 9H, Ar-H), 8.4 (d, J=8.1 Hz, 1H, C ₉ -H), 8.45 (d, J=8.1 Hz, 1H, C ₁₀ -H), 9.2 (s, 1H, C ₄ -H); MS: (m/z) 336 M ⁺ .
7	219	85	C ₁₇ H ₁₅ N ₃ O ₃ S ₂ (373.46)	54.55 (54.69)	4.00 (4.02)	11.24 (11.26)	IR: 3340 (NH ₂), 3150(NH), 2220 (CN), 1680cm ⁻¹ (C=O, amidic); ¹ H-NMR (CDCl ₃) δ 3.7(s, 2H, CH ₂), 6.2 (br, 2H, CONH ₂ exchangeable with D ₂ O), 7.2-7.98 (m, 10H, Ar-H), 9.25 (s, 1H, NH exchangeable with D ₂ O); MS: (m/z) 373 M ⁺ .
8	145	62	C ₁₇ H ₁₅ N ₃ O ₃ S ₂ (373.46)	45.51 (45.50)	4.01 (4.02)	11.23 (11.26)	IR: 3450 (NH ₂), 3150(NH), 1661 (CO), 1550 (Ph), 1270, 1180cm ⁻¹ (SO ₂); ¹ H-NMR (CDCl ₃) δ 5.5 (br, 2H, NH ₂ exchangeable with D ₂ O), 6.2 (br, 2H, CONH ₂ exchangeable with D ₂ O), 7.4-8.0 (m, 10H, Ar-H), 8.6 (s, 1H, NH exchangeable with D ₂ O); MS: (m/z) 373 M ⁺ .
10	154	88	C ₂₃ H ₁₈ N ₂ O ₃ S ₂ (434.54)	63.50 (63.59)	4.12 (4.14)	6.43 (6.45)	IR: 3463 (NH ₂), 3194(NH), 1720 (CO), 1587cm ⁻¹ (Ph); ¹ H-NMR (CDCl ₃) δ 6.5 (br, 2H, NH ₂ exchangeable with D ₂ O), 7.3-8.1 (m, 15H, Ar-H), 9.22 (s, 1H, NH exchangeable with D ₂ O); MS: (m/z) 434 M ⁺ .

Continuation of the Table 1.

No.	mp° C	Yld %	Mol. formula	Analysis Calcd. (Found %)			Characterization
				C	H	N	
11	190	94	C ₁₈ H ₁₆ N ₂ O ₃ S ₂ (372.47)	58.00 (58.06)	4.29 (4.30)	7.50 (7.52)	IR: 3287(NH), 2220 (CN), 1730 (CO), 1603 cm ⁻¹ (Ph); ¹ H-NMR (CDCl ₃) δ 2.3 (s, 3H, CH ₃), 3.7 (s, 2H, CH ₂), 7.16-7.97 (m, 10H, Ar-H), 9.25 (s, 1H, NH exchangeable with D ₂ O); MS: (m/z) 372 M ⁺ .
12	165	88	C ₁₈ H ₁₆ N ₂ O ₃ S ₂ (372.47)	58.10 (58.06)	4.28 (4.30)	7.51 (7.52)	IR: 3456 (NH ₂), 3288 (NH), 1730 (CO), 1603cm ⁻¹ (Ph); ¹ H-NMR (CDCl ₃) δ 2.14 (s, 3H, CH ₃), 5.3 (br, 2H, NH ₂ exchangeable with D ₂ O), 7.26-7.96 (m, 10H, Ar-H), 9.25 (s, 1H, NH exchangeable with D ₂ O); MS: (m/z) 372 M ⁺
13	188	80	C ₁₇ H ₁₃ N ₃ O ₂ S ₂ (355.44)	57.33 (57.46)	3.65 (3.66)	11.82 (11.83)	IR: 3200 (NH), 2220, 2195 (two CN), 1603 cm ⁻¹ (Ph); ¹ H-NMR (CDCl ₃) δ 3.23 (s, 2H, CH ₂), 7.12-7.87 (m, 10H, Ar-H), 9.25 (s, 1H, NH exchangeable with D ₂ O); MS: (m/z) 355M ⁺ .
14	158	66	C ₁₇ H ₁₃ N ₃ O ₂ S ₂ (355.44)	57.29 (57.46)	3.63 (3.66)	11.81 (11.83)	IR: 3456 (NH ₂), 3266 (NH), 2220 (CN), 1603cm ⁻¹ (Ph); ¹ H-NMR (CDCl ₃) δ 6.5 (br, 2H, NH ₂ exchangeable with D ₂ O), 7.31-7.96 (m, 10H, Ar-H), 8.7 (s, 1H, NH exchangeable with D ₂ O); MS: (m/z) 355M ⁺ .
15	248	93	C ₁₉ H ₁₈ N ₂ O ₄ S ₂ (402.49)	56.66 (56.71)	4.46 (4.47)	6.95 (6.96)	IR: 3278(NH), 2220 (CN), 1730 cm ⁻¹ (CO); ¹ H-NMR (CDCl ₃) δ 1.3 (t, J=2.5 Hz, 3H, CH ₃), 3.7 (s, 2H, CH ₂), 4.3 (q, J=2.5Hz, 2H, CH ₂), 7.5- 8.56 (m, 10H, Ar-H), 9.25 (s, 1H, NH exchangeable with D ₂ O); MS: (m/z) 402 M ⁺ .
16	152	86	C ₁₉ H ₁₈ N ₂ O ₄ S ₂ (402.50)	56.70 (56.71)	4.45 (4.47)	6.94 (6.96)	IR: 3448 (NH ₂), 3243(NH), 1730 (CO), 1603cm ⁻¹ (Ph); ¹ H-NMR (CDCl ₃) δ 1.26 (t, J= 2.5 Hz, 3H, CH ₃), 4.22 (q, J=2.5Hz, 2H, CH ₂), 6.55 (br, 2H, NH ₂ exchangeable with D ₂ O), 7.18-7.96 (m, 10H, Ar-H), 9.25 (s, 1H, NH exchangeable with D ₂ O); MS: (m/z) 402 M ⁺ .

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Samples Availability: available from the authors.