N,N-dimethylformamide-promoted reaction of isocyanides and barbituric acids: an easy synthesis of 5-[(alkyl or arylamino)methylene]barbituric acids

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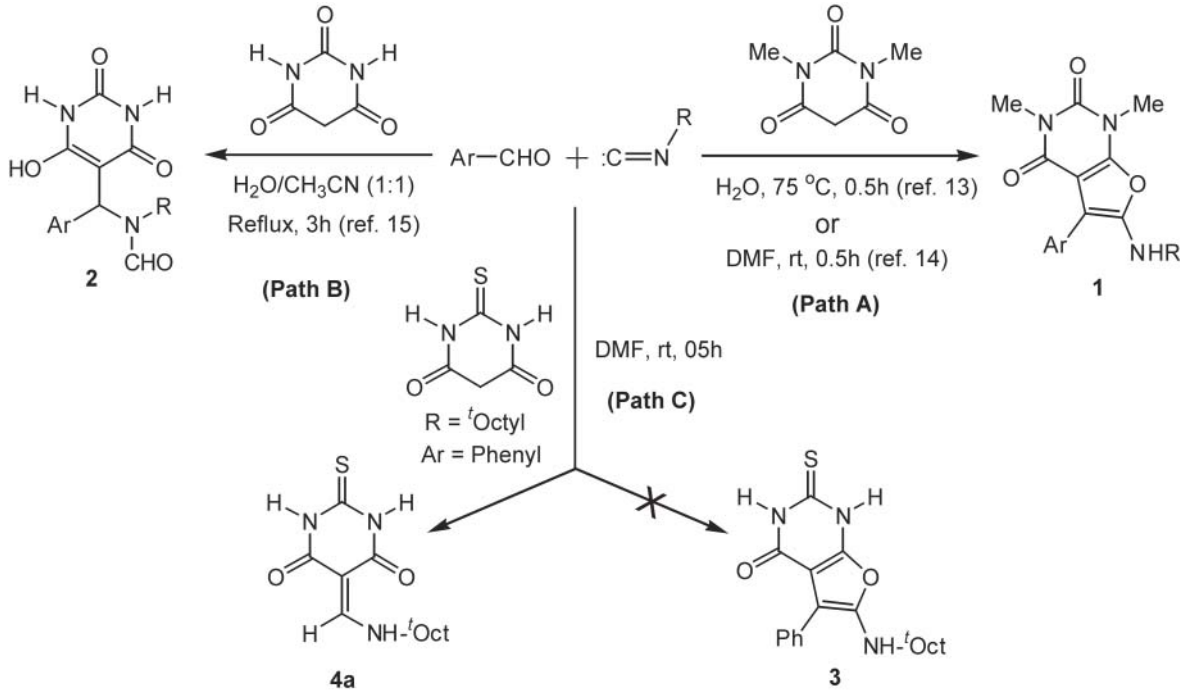
N,N-dimethylformamide promoted the reaction of alkyl or arylisocyanides with barbituric acid derivatives which led to 5-[(alkyl or arylamino)methylene]barbituric acids in good yields at room temperature. The work-up of reactions was very simple and the crude products were sufficiently pure to be used without further purification. This procedure provides an alternative method for the synthesis of aminomethylenebarbituric acids.

Keywords: barbituric acid, *N,N*-dimethylformamide, heterodiene, isocyanide

Among three chemical characteristics of isocyanides, the α-addition, the α-acidity and the easy formation of radicals, the first has attracted the most attention of organic chemists.[1] The α-addition by nucleophiles and electrophiles on the carbon atom of the isocyano functionality is the main characteristic of isocyanides with other common organic functional groups. The formal divalency of the isocyanides provides a challenge to the successful development of the α-addition reactions.[2,3] All reactions of isocyanides are conversions of divalent carbon atoms into products with tetravalent carbon atoms.[4,5]

The reactions of 1,3-dicarbonyl compounds with isocyanides[6–11] and isocyanates[12] are well documented. In our earlier publications,[13,14] we described two relatively facile routes to fused furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **1**. These compounds were obtained by treatment of 1,3-dimethylbarbituric acid with aromatic aldehydes and isocyanides in hot water[13] or small amount of *N,N*-dimethylformamide (DMF) at room temperature[14] (Scheme 1, Path A). Based on the three-component reaction, more efforts were made to investigate the reactions of unsubstituted barbituric acid. In 2007, some unexpected results were obtained when barbituric acid was used.[15] The condensation reactions between alkyl isocyanide, substituted benzaldehydes and barbituric acid were performed in water/acetonitrile (1:1) under reflux conditions to give *N*-alkyl-*N*-[aryl-(2,4,6-trioxohexahydropyrimidin-5-yl)methyl]formamides **2** in 3 h (Scheme 1, Path B).

During an attempt to prepare 6-(*tert*-octylamino)-5-phenyl-2-thioxo-2,3-dihydrofuro[2,3-*d*]pyrimidin-4(1*H*)-one **3** from *tert*-octyl isocyanide, benzaldehyde, and 2-thiobarbituric acid in DMF, a white crystalline solid precipitated from the reaction mixture when left to stand 30 min at room temperature (Scheme 1, Path C). Structural elucidation by ^{1}H and ^{13}C NMR spectroscopy revealed this precipitate to be 5-[(*tert*-octylamino) methylene]-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione **4a** without the participation of benzaldehyde, which did not enter into the reaction. This interesting result led us to further investigate the scope of this methodology to access 5-[(alkyl or ary lamino)methylene]barbituric acids. Here we report an efficient reaction of isocyanides and barbituric acids in DMF at room temperature which afforded methylenebarbituric acids.



Scheme 1

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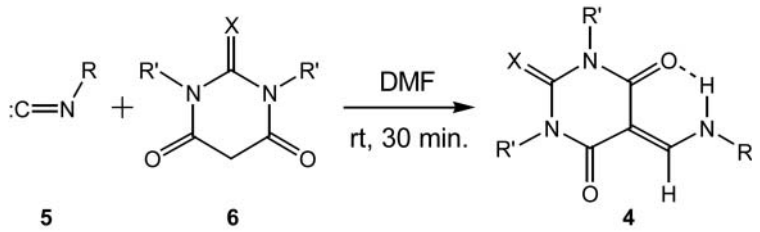
The condensation reactions of alkyl or aryl isocyanides **5** with barbituric acid derivatives **6** proceeded spontaneously at room temperature in a small amount of DMF and were completed after 30 min to afford corresponding 5-[(alkyl or arylamino)methylene]barbituric acid derivatives **4** in good isolated yields (Scheme 2). The results are summarised in Table 1.

The scope and limitations of this reaction were explored using four barbituric acid derivatives and six alkyl or aryl isocyanides. It was found that 2-thiobarbituric acid, 1,3-diethyl-2-thiobarbituric acid, barbituric acid and 1,3-dimethylbarbituric acid can tolerate the reaction conditions with good yields. Also, the results show that the reaction is quite general with a variety of structurally diverse alkyl or aryl isocyanides affording the expected products **4**.

The ^{1}H NMR spectrum of **4a** exhibited three single sharp line readily recognised as arising from two *tert*-butyl (δ_H 0.92 ppm), two geminal methyl groups (δ_H 1.40 ppm) and



5 **6** **4**

Scheme 2

Table 1 Synthesis of aminomethylenebarbituric acids **4a–1** in DMF

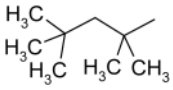
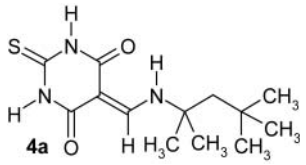
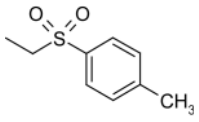
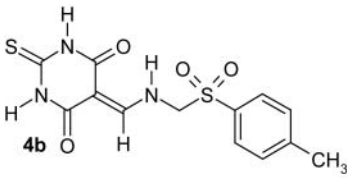
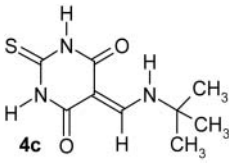
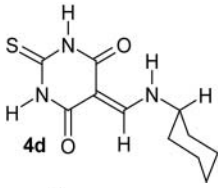
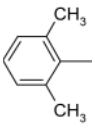
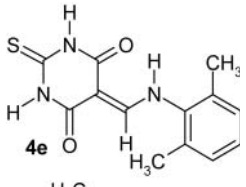
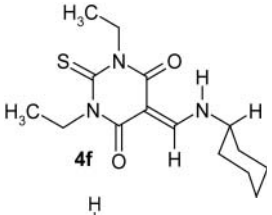
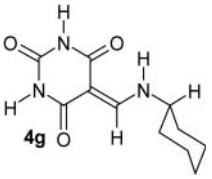
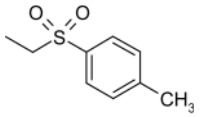
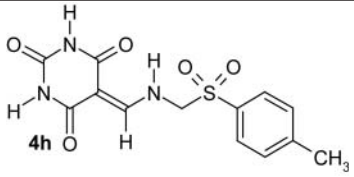
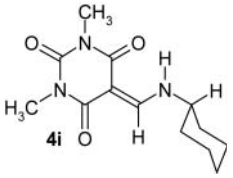
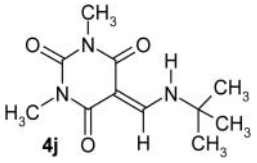
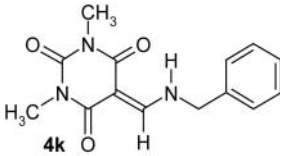
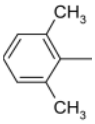
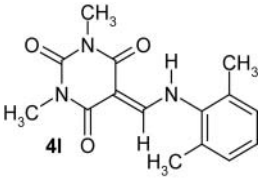
Entry	R	R′	X	Product	Yield[a]/%
1		H	S	 **4a**	91
2		H	S	 **4b**	88
3		H	S	 **4c**	91
4		H	S	 **4d**	93
5		H	S	 **4e**	85
6			S	 **4f**	84
7		H	O	 **4g**	84

Table 1 *Continued*

Entry	R	R′	X	Product	Yield[a]/%
8		H	O	 **4h**	80
9		CH_3—	O	 **4i**	83
10		CH_3—	O	 **4j**	90
11		CH_3—	O	 **4k**	81
12		CH_3—	O	 **4l**	83

[a] Refers to isolated yield. The products **4c**, **4d**, **4e**, **4i**, **4j**, **4k** and **4l** have been already prepared.[9,11]

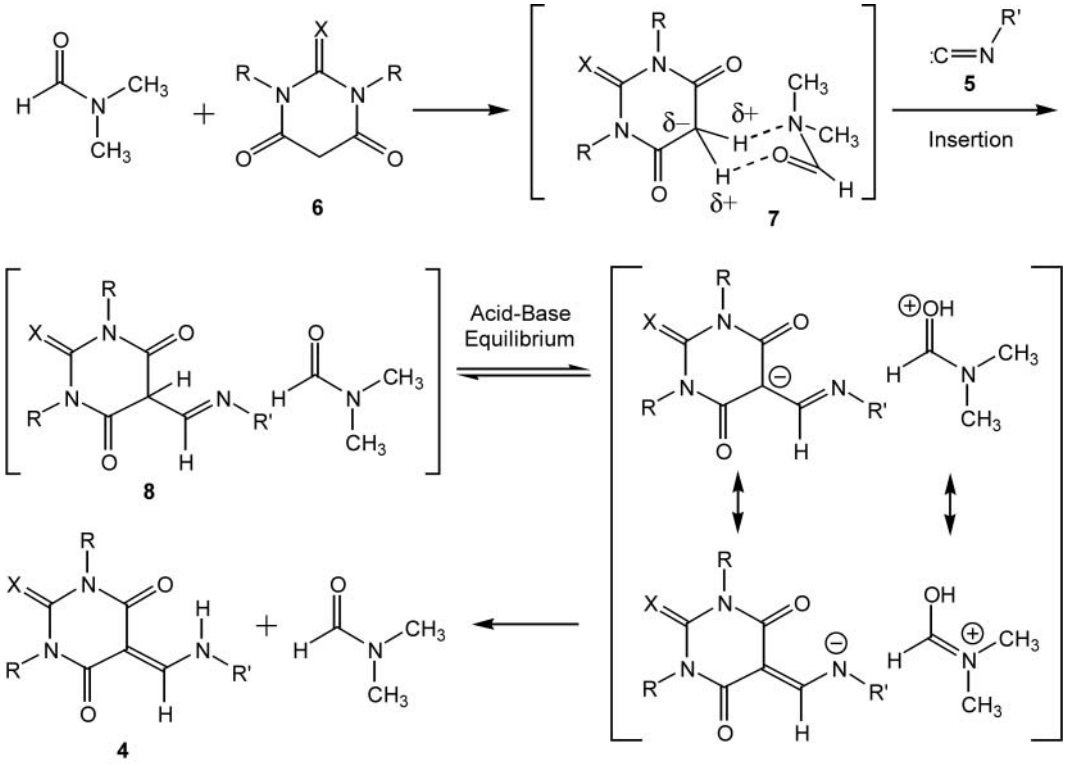
two methylene protons (δ_H 1.65 ppm) along with a doublet (δ_H 8.14 ppm, $^3J_{HH}$ = 15.0 Hz) for the vinylic methine. A fairly broad doublet (δ_H 10.78 ppm, $^3J_{HH}$ = 15.0 Hz) is observed for the enamine NH group. The vicinal proton–proton coupling constant ($^3J_{HH}$) as a function of torsion angle can be obtained from the Karplus equation.[16] Observation of $^3J_{HH}$ = 15.0 Hz for two vicinal protons (NH–CH=) in compound **4a** indicates a *trans* arrangement for these centres. Furthermore, the chemical shift of the NH group indicates that this moiety must have participated in a six-membered intramolecular hydrogen bond formation with the vicinal carbonyl group as shown in Scheme 2. Two singlets (δ_H 11.81 and 11.91 ppm) were observed for the two NH groups of thiobarbituric moiety.

The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed 10 distinct resonances in agreement with the suggested structure. Partial assignment of these resonances is given in experimental section.

High rates of reactions at room temperature have enabled us to establish a significant catalytic role for DMF in reaction of barbituric acids with isocyanides. A reasonable possibility for DMF-catalysed reaction has been suggested in Scheme 3. The first step may involve formation of a six-membered cyclic chair-like intermediate **7**. In this situation, the insertion of isocyanide **5** into the C–H bond of barbituric acid **6** is facilitated by strong attraction of active hydrogens with highly electronegative oxygen and nitrogen atoms of DMF moiety (double non-conventional hydrogen bonds)[17,18] in intermediate **7** to form 5-[(alkyl or arylimino)methyl]babituric acid **8** as a strong CH-acid. As shown in Scheme 3, DMF as a bidentate weak base can catalyse the imine-enamine tautomerisation of strong CH-acid **8** to 5-[(alkyl or arylamino)methylene]barbituric acid **4** as a weaker NH-acid.

In order to confirm that the reaction was truly catalysed by DMF, we carried out many parallel experiments. We examined the reaction of *tert*-octyl isocyanide with 2-thiobarbituric acid in the presence of catalytic amount (50 mol%) of DMF. The desired product **4a** was isolated in 95% yield after 30 min at room temperature. Very low amounts of **4a** (<5%) obtained in the absence of DMF under similar reaction conditions. Furthermore, we examined the above-mentioned reaction in the presence of catalytic amount (50 mol%) of DMSO as another polar aprotic solvent. The reaction gave product **4a** of less than 10%. While, this reaction in the presence of 50 mol% of *N,N*-dimethylacetamide (DMAc) or *N*-methylpyrrolidone (NMP) formed **4a** in 83% and 80% isolated yields, respectively. These results highlighted the decisive role of DMF, DMAc and NMP (*N,N*-substituted amidic polar solvents) on the efficiency of the reaction.

In summary, we have reported the synthesis of 5-[(alkyl or arylamino)methylene]barbituric acids via a DMF-promoted reaction between barbituric acid derivatives and alkyl or aryl isocyanides at room temperature in 30 min. The main advantages of this methodology with respect to the other methods[9,11,12,19–22] are: (i) the reaction is simple to perform; (ii) the reaction occurs at room temperature; (iii) the yields are good to high; (iv) there is no need for any other catalyst; (v) the reaction completes within a short period of time; and (vi) purification of the products is not necessary.



Scheme 3

Experimental

Melting points were measured on a Büchi 535 apparatus and are uncorrected. Elemental analyses were performed using an Elementar Vario EL III instrument. FT-IR Spectra were recorded on a Bruker Equinox-55 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 Avance spectrometer at 500.1 and 125.8 MHz, respectively, with $CDCl_3$ or CD_3SOCD_3 as solvents and calibrated using residual undeuterated solvent as an internal reference. Chemical shifts are reported in parts per million relative to TMS as internal reference. Analytical TLC was carried out on pre-coated plates (Merck silica gel 60, F254) and visualised with UV light. All chemical reagents were obtained from Aldrich, Merck or Acros and were used without further purification. The products **4c–4e** and **4i–4l** are known compounds, which were identified by IR and ^{1}H NMR spectral data and comparing their melting points with literature reports.[11,13]

Typical procedure for the preparation of **4a**

To a solution of 2-thiobarbituric acid (0.144 g, 1.0 mmol) in DMF (0.5 mL) in a screw-capped vial was added *tert*-octyl isocyanide (0.140 g, 1 mmol) via a syringe and was shaken for 1 min. The reaction mixture was then kept for about 30 min at room temperature (25 °C) and the completion of reaction was confirmed by TLC (EtOAc–hexane 1:1). Then, the resulting solids were filtered and washed with diethyl ether (10 mL) to yield **4a** as white powder (0.257 g, 91 %). The dried product thus obtained showed a single spot on TLC and was pure enough for all analytical purposes.

5-{[(1,1,3,3-Tetramethylbutyl)amino]methylene}-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (4a): M.p. 282–284 °C; IR (KBr) (ν_{max}/cm^{-1}): 3456, 3112 (N–H), 1687, 1621 (C=O), 1162 (C=S); ^{1}H NMR (500.1 MHz, DMSO-d_6): δ_H 0.92 (9 H, s, CMe_3), 1.40 (6 H, s, CMe_2), 1.65 (2 H, s, CH_2), 8.14 (1 H, d, $^{3}J_{HH}$ = 15.0 Hz, NH–C*H*=), 10.78 (1 H, d, $^{3}J_{HH}$ = 15.0 Hz, N*H*. . .O=C), 11.81 and 11.91 (2 H, 2 s, *H*NCSN*H*); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ_C 177.5 (C=S), 164.1 and 161.6 (2 C=O), 154.9 (N*C*H=C), 91.1 (NCH=*C*), 58.3 (CH_2), 53.9 (*C*Me$_2$), 31.3 (*C*Me$_3$), 31.0 (C*Me$_3$), 28.6 (C*Me$_2$); Anal. Calcd for $C_{13}H_{21}N_3O_2S$ (283.39): C, 55.10; H, 7.47; N, 14.83. Found: C, 55.22; H, 7.39; N, 14.95%.

5-[({[(4-Methylphenyl)sulfonyl]methyl}amino)methylene]-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (4b): White powder (0.298 g, 88 %); m.p. 315–317 °C; IR (KBr) (ν_{max}/cm^{-1}): 3403, 3288, 3220 (N–H), 1705, 1655 (C=O), 1620 (C=C), 1363, 1141 (SO_2), 1138 (C=S); ^{1}H NMR (500.1 MHz, DMSO-d_6): δ_H 2.44 (3 H, s, CH_3), 5.12 (1 H, d, $^{3}J_{HH}$ = 6.6 Hz, SO_2CH_2NH), 7.48 and 7.67 (4 H, 2 d, $^{3}J_{HH}$ = 8.7 Hz, C_6H_4), 8.04 (1 H, d, $^{3}J_{HH}$ = 14.1 Hz, NH–C*H*=), 10.27 (1 H, m, N*H*…O=C), 11.92 and 12.00 (2 H, 2 s, *H*NCSN*H*); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ_C 178.1 (C=S), 163.4 and 161.4 (2 C=O), 160.0 (N*C*H=C), 145.4, 133.2, 130.1 and 128.8 (arom. carbons), 94.1 (NCH=*C*), 67.4 (SO_2CH_2), 21.1 (CH_3); Anal. Calcd for $C_{13}H_{13}N_3O_4S_2$ (339.39): C, 46.01; H, 3.86; N, 12.38. Found: C, 45.73; H, 3.83; N, 12.42%.

5-[(Cyclohexylamino)methylene]-1,3-diethyl-2-thioxodihydropyrimidine-4,6 (1H,5H)-dione (4f): White powder (0.260g, 84 %); m.p. 129–131 °C; IR (KBr) (ν_{max}/cm^{-1}): 3434 (N–H), 1685, 1647 (C=O) 1607 (C=C), 1106 (C=S); ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H 1.24 and 1.26 (3 H, 2 t, $^{3}J_{HH}$ = 6.9 Hz, 2 CH_2CH_3), 1.30–2.00 (10 H, m, 5 CH_2), 3.39 (1 H, m, NCH), 4.49 and 4.51 (4 H, 2 q, $^{3}J_{HH}$ = 6.9 Hz, 2 CH_2CH_3), 8.25 (1 H, d, $^{3}J_{HH}$ =14.6 Hz, NH–C*H*=), 10.60 (1 H, br s, N*H*. . .O=C); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C (ppm) 178.9 (C=S), 163.1 and 161.1 (2 C=O), 158.3 (N*C*H=C), 92.6 (NCH=*C*), 59.1 NCH), 42.8 and 42.2 (2 CH_2), 33.4, 24.9 and 24.2 (5 CH_2), 12.4 and 12.3 ($2CH_3$); Anal. Calcd for $C_{15}H_{23}N_3O_2S$ (309.42): C, 58.22; H, 7.49; N, 13.58. Found: C, 58.39; H, 7.53; N, 13.49%.

5-[(Cyclohexylamino)methylene]pyrimidine-2,4,6(1H,3H,5H)-trione (4g): White powder (0.199 g, 84 %); m.p. 278–280 °C; IR (KBr) (ν_{max}/cm^{-1}): 3434, 3193, 3083 (N–H), 1705, 1667, 1644 (C=O); ^{1}H NMR (500.1 MHz, DMSO-d_6): δ_H (ppm) 1.37–1.86 (10 H, m, 5CH_2), 3.52–3.54 (1 H, m, NHC*H*), 8.14 (1 H, d, $^{3}J_{HH}$ = 14.6 Hz, NH–C*H*=), 10.17(1 H, dd, $^{3}J_{HH}$ = 14.6 Hz, $^{3}J_{HH}$ = 7.7 Hz, N*H*…O=C), 10.52 and 10.64 (2 H, 2 s, *H*NCON*H*); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ_C (ppm) 166.1 and 163.7 (2 HN–C=O), 156.6 (N*C*H=C), 150.8 (HNCONH), 89.2 (NCH=*C*), 57.7 (NHCH), 32.5, 24.4 and 24.0 (5 CH_2 of cyclohexyl); Anal. Calcd for $C_{11}H_{15}N_3O_3$ (237.25): C, 55.69; H, 6.37; N, 17.71. Found: C, 56.08; H, 6.42; N, 17.59%.

5-[({[(4-Methylphenyl)sulfonyl]methyl}amino)methylene]pyrimidine-2,4,6(1H,3H,5H)-trione (4h): White powder (0.258 g, 80 %); m.p. 298–300 °C; IR (KBr) (ν_{max}/cm^{-1}): 3454, 3238 (N–H), 1693, 1649 (C=O), 1358, 1147 (SO_2); ^{1}H NMR (500.1 MHz,DMSO-d_6): δ_H (ppm) 2.41 (3 H, s, CH_3), 5.10 (1 H, s, SO_2CH_2NH), 7.48 and 7.67 (4 H, 2 d, $^{3}J_{HH}$ = 8.1 Hz, C_6H_4), 8.00 (1 H, s, NH–C*H*=), 10.10 (1 H, m, N*H*…O=C), 10.74 and 10.80 (2 H, 2 br s, *H*NCON*H*); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ_C (ppm) 165.7 and 163.3 (2 HN–C=O), 159.1 (N*C*H=C), 150.6 (HNCONH), 145.3, 133.3, 130.0 and 128.7 (arom. carbons), 92.6 (NCH=*C*), 67.3 (SO_2CH_2), 21.1 (CH_3); Anal. Calcd for

$C_{13}H_{13}N_3O_5S$ (323.32): C, 48.29; H, 4.05; N, 13.00. Found: C, 48.12; H, 4.09; N, 12.94%.

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