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A convenient synthesis of sulfonylureas from carboxylic acids and sulfonamides via an in situ Curtius rearrangement

Christopher A. Luckhurst,* Ian Millichip, Beth Parker, James Reuberson and Mark Furber

Department of Medicinal Chemistry, AstraZeneca R&D Charnwood, Loughborough, Leicestershire, England LE11 5RH, United Kingdom

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Abstract—A one-pot reaction of carboxylic acids with sulfonamides to afford sulfonylureas is described.

1. Introduction

As part of a medicinal chemistry programme, targeting the zinc metalloproteinase endothelin converting enzyme (ECE-1), a range of thiazole sulfonylureas were synthesised to profile their biological activity.

Sulfonylureas are employed in a variety of applications including that of the treatment of type II diabetes (for example, tolbutamide and glibenclamide, Fig. 1), and as plant growth regulators or herbicides.

The limited availability of isocyanates meant that a number of the methodologies known in the literature to generate sulfonylureas were explored (Scheme 1).[1]

Neither the reaction of a pre-formed sulfonyl isocyanate with an amino thiazole, nor that of a thiazole isocyanate with a sulfonamide was successful (Scheme 1). Furthermore, the formation of a primary urea from the amino thiazole using sodium cyanate followed by reaction with a sulfonyl chloride met with little success. The procedure shown in Scheme 2, via an activated sulfonyl carbamate, was also dropped in the quest for a more direct method

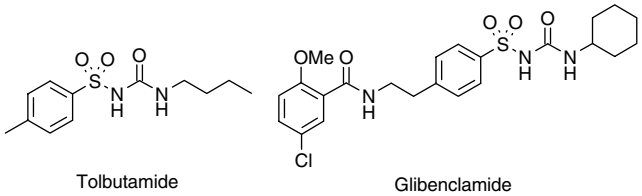
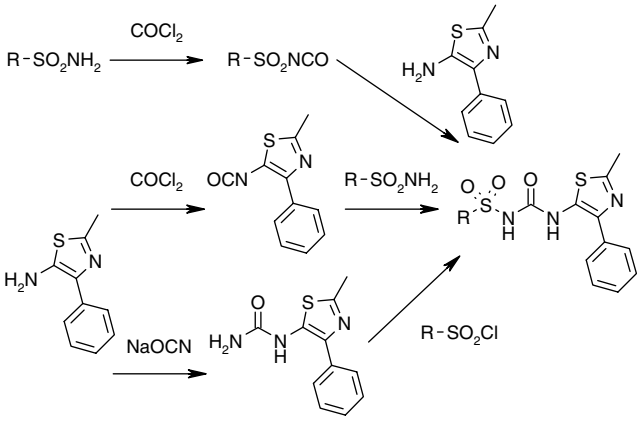
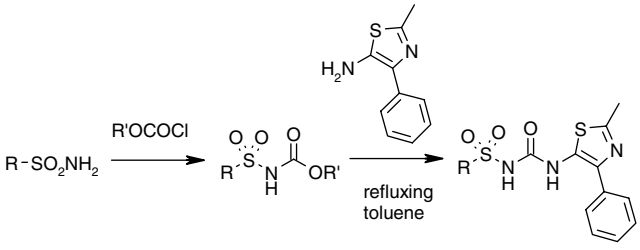


Figure 1. Sulfonylurea drugs used in the treatment of type II diabetes.



Scheme 1. Some early attempts at the synthesis of thiazole sulfonylureas.



Scheme 2. Sulfonylureas from sulfonyl carbamates.

* Corresponding author. Tel.: +44 1509 644542; fax: +44 1509 645571; e-mail: chris.luckhurst@astrazeneca.com

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that would enable a large number of compounds to be synthesised in a very short time.

2. Results and discussion

Generally, the wide range of methodologies[1] for the synthesis of sulfonylureas are much more cumbersome than the procedure described in this Letter. As outlined above, the application of some of these methods to the thiazole system described proved unsuccessful. Their failure may in part be a consequence of the instability of the thiazole isocyanate present as an intermediate in some of these methods. The method presented in this Letter avoids this problem by generating and reacting the isocyanate in situ.

The sulfonylureas were accessed conveniently from the corresponding sulfonamides and carboxylic acids via the generation of isocyanates in situ. Diphenylphosphoryl azide (DPPA) was employed to form the acyl azide from the acid, and then the isocyanate via Curtius rearrangement, in the presence of a sulfonamide. This clearly obviates the requirement to isolate isocyanates or other intermediates and attempts to limit the problem of competing isocyanate hydrolysis. A wide range of carboxylic acids are available commercially, and those that are not are much easier to obtain through synthesis than their isocyanate counterparts. The reactions were initially carried out at 85 °C in the presence of triethylamine or diisopropylethylamine as base, in benzene. The product sulfonylureas were isolated either by silica gel chromatography, by trituration with acetonitrile or ethyl acetate, or by reverse phase HPLC. The main byproduct was the symmetrical urea, and accordingly some sulfonamide was recovered.

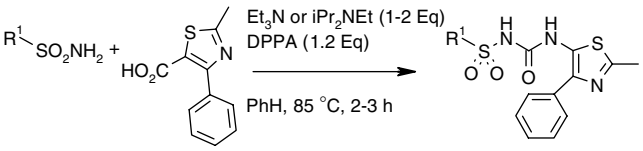
The scope of the reaction is illustrated by the compounds in Table 1. Heteroaromatic and benzylic sulfonamides underwent reaction with 2-methyl-4-phenyl-1,3-thiazole-5-carboxylic acid in synthetically useful isolated yields.

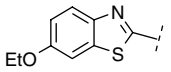
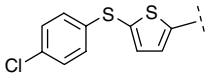
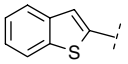
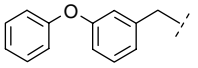
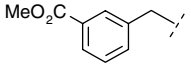
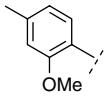
To explore the chemistry more generally and investigate steric and electronic effects in the sulfonamide and carboxylic acid, a small range of simple sulfonylureas was synthesised. The reaction of methanesulfonamide with benzoic acid to furnish sulfonylurea **7** was more successful than those with aryl sulfonamides and benzoic acid, reflecting the reactivity of the sulfonamide (Table 2).

Attention was next turned to the reaction of methanesulfonamide with a range of aromatic carboxylic acids, as illustrated in Table 3. An alternative procedure was attempted, whereby the starting materials were heated at 85 °C in the presence of potassium carbonate in dioxane.

Generally, the yields obtained with this method were similar to those from the *N*,*N*-diisopropylethylamine-benzene method described above; in Table 3, the method with the higher yield is shown for each example.

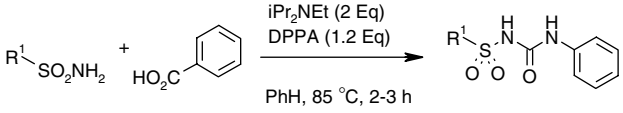
Table 1. Reaction of sulfonamides with 2-methyl-4-phenyl-1,3-thiazole-5-carboxylic acid to give sulfonylureas

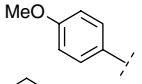
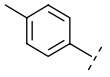


R^1	Product	Isolated yield[a] (%)
	**1**	67
	**2**	62
	**3**	48[b]
	**4**	41
	**5**	41
	**6**	30

[a] >95% chemical purity as determined by analytical HPLC.
[b] More carboxylic acid (0.3 equiv) was added after 3 h, heating continued for a further 2 h.

Table 2. Reaction of sulfonamides with benzoic acid

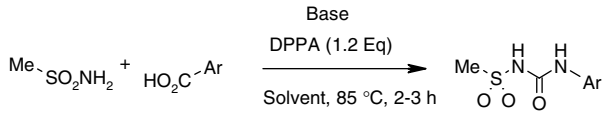


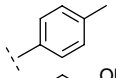
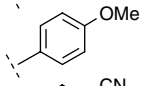
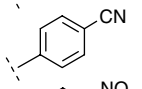
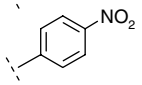
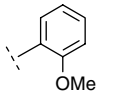
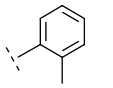
R^1	Product	Isolated yield (%)
	**7**	77
	**8**	43
	**9**	33
	**10**	31

ortho-Substitution on the aromatic acid resulted in lower yields than *para*-substitution. Not illustrated in the table, electron-rich heterocyclic acids fared poorly; 2-furoic acid gave a yield of only 18% under the diisopropylamine-benzene conditions and no conversion with potassium carbonate–dioxane. No conversion to sulfonylurea was observed for pyrrole-2-carboxylic acid with either method.

For aliphatic acids, the alternative potassium carbonate–dioxane conditions proved to be far superior to the procedure using diisopropylamine-benzene (Table

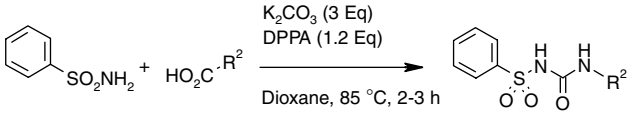
Table 3. Reactions of methanesulfonamide with benzoic acids

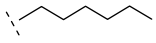
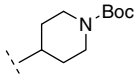
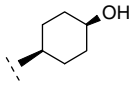


Ar	Product	Base[a]	Solvent	Isolated yield (%)
	**11**	*i*-Pr_2NEt	C_6H_6	62
	**12**	K_2CO_3	Dioxane	51
	**13**	*i*-Pr_2NEt	C_6H_6	36[b]
	**14**	K_2CO_3	Dioxane	34
	**15**	*i*-Pr_2NEt	C_6H_6	32
	**16**	*i*-Pr_2NEt	C_6H_6	22

[a] 2 equiv of *i*-Pr_2NEt, or 3 equiv of K_2CO_3 were used.
[b] For example, using K_2CO_3, dioxane, the yield of **13** was 29%.

Table 4. Reaction of aliphatic acids with benzenesulfonamide



R^2	Product	Isolated yield (%)
	**17**	52
	**18**	50
	**19**	40
	**20**	23

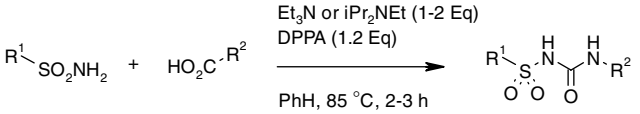
4). Entry **20** demonstrates that an unprotected hydroxyl group can be tolerated, albeit in lower yield.

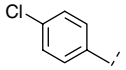
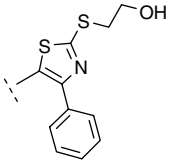
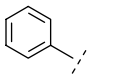
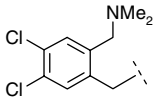
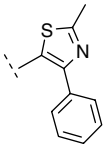
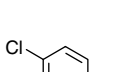
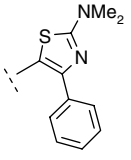
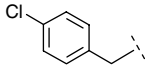
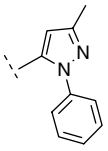
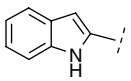
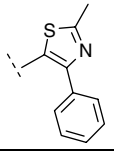
As illustrated by some of the examples in Table 5, yields were lower when certain functionalities were present, but this methodology clearly allows examples incorporating nitrogen atoms and hydroxyl groups to be synthesised. This route was a convenient, if only moderate-yielding method to access these more functionalised compounds. Evidently, a multi-step route involving isolation of the isocyanate would be incompatible with some of the functionality in the desired products. In general, the reaction of sulfonamides with the more electron-rich heterocycle 3-methyl-1-phenyl-1*H*-pyrazole-5-carboxylic acid gave lower yields of the sulfonylureas; one example, **25**, is shown in Table 5.

The reaction was also attempted with an amide in the place of the sulfonamide as shown in Scheme 3, furnishing acyl urea **27** in a useful 32% yield.

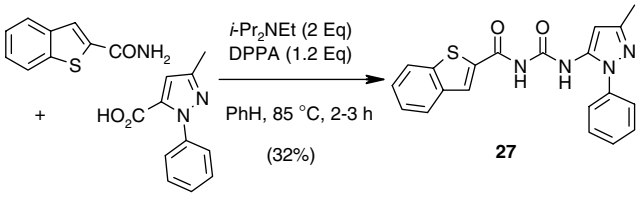
Many of the sulfonamides that we wished to use in the programme of work directed towards ECE inhibitors

Table 5. Formation of sulfonylureas from heterocyclic acids



R^1	R^2	Product	Isolated yield[a] (%)
		**21**	30
		**22**	30
		**23**	29
		**24**	27
		**25**	25
		**26**	15

[a] >95% chemical purity as determined by analytical HPLC.

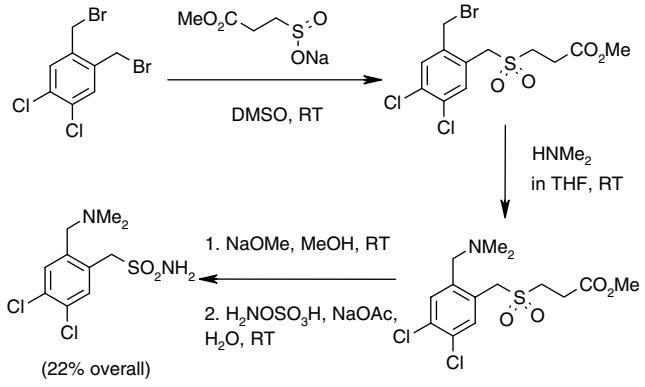


Scheme 3. Formation of an acyl urea.

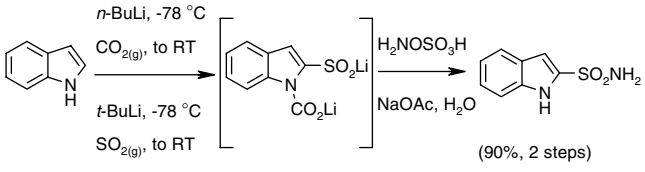
are unavailable commercially and are needed to be synthesised. Alkylsulfonamides were generated from the corresponding halide via the sulfinate salt using sodium 3-methoxy-3-oxopropane-1-sulfinate (SMOPS)[2,3] and subsequent treatment with hydroxylamine-*O*-sulfonic acid as an electrophilic nitrogen source. For aromatic and heteroaromatic sulfonamides, lithiation followed by quenching with sulfur dioxide and then hydroxylamine-*O*-sulfonic acid also proved to be efficient. Scheme 4 describes the synthesis of an aminoalkyl benzenesulfonamide from SMOPS, used in the synthesis of zwitterionic sulfonylurea **23**.

Scheme 5 shows a facile synthesis of indole-2-sulfonamide en route to **26**, based upon methodology from Katritzky,[4] avoiding the requirement for protection of the indole nitrogen, with, for example, a phenyl sulfonyl group.

In summary, this methodology enabled a wide variety of sulfonylureas to be obtained that would not have been accessed conveniently by other means. The reactivity of both the sulfonamide and acid were the key determinants to the product yield. Isocyanate trapping is the major constraint to the methodology with the weak sulfonamide nucleophile. The main byproduct seen was the symmetrical urea which was presumably formed from reaction of the in situ-formed isocyanate with its amine hydrolysis product; however, the addition of molecular sieves failed to provide a significant improvement in the yield of the sulfonylureas. Additionally, performing the reaction up to the same temperature under microwave irradiation in a sealed tube offered no enhancement in yield versus the thermal conditions described above. It appears unlikely that the sulfonamide is reacting directly with DPPA, or competing with azide in the reaction with the activated acid moiety. Efforts are underway to explore the use of solid-supported DPPA[5] to expedite removal of phosphorus-containing byproducts.



Scheme 4.



Scheme 5.

3. Procedures for the synthesis of sulfonylureas

3.1. The synthesis of sulfonylureas using triethylamine or *N*,*N*-diisopropylethylamine-benzene

3.1.1. Preparation of 6-ethoxy-*N*-{[(2-methyl-4-phenyl-1,3-thiazol-5-yl)amino]carbonyl}-1,3-benzothiazole-2-sulfonamide (1). To a stirred mixture of 2-methyl-4-phenyl-1,3-thiazole-5-carboxylic acid (0.132 g), 6-ethoxy-1,3-benzothiazole-2-sulfonamide (0.163 g) and triethylamine (0.100 mL) in benzene (5 mL) was added diphenylphosphoryl azide (0.155 mL) under nitrogen. The mixture was then heated at 85 °C for 2 h. The cooled mixture was concentrated in vacuo, dissolved in a small volume of acetonitrile and subjected to reverse phase HPLC (SunFire®, 5% to 90% acetonitrile in 0.1% v/v aqueous trifluoroacetic acid). The appropriate fractions were concentrated in vacuo to give **1** (0.190 g, 67%) as a white solid; mp 174–176 °C; ^{1}H NMR (400 MHz, DMSO) δ 9.34 (s, 1H), 8.07 (d, $J = 8.7$ Hz, 1H), 7.81 (d, $J = 2.6$ Hz, 1H), 7.70 (d, $J = 7.4$ Hz, 2H), 7.43 (t, $J = 7.8$ Hz, 2H), 7.34 (t, $J = 7.4$ Hz, 1H), 7.26 (dd, $J = 9.2$, 2.6 Hz, 1H), 4.14 (q, $J = 6.9$ Hz, 2H), 2.56 (s, 3H), 1.38 (t, $J = 6.9$ Hz, 3H); one NH resonance absent; ^{13}C NMR (125.7 MHz, DMSO) δ 159.9, 158.2, 145.7, 138.2, 133.3, 132.6, 128.6, 128.4, 127.5, 126.8, 125.2, 121.3, 118.0, 114.8, 105.1, 63.9, 18.5, 14.4; LRMS (ESI) m/z 475 $[M+H]^+$, 473 $[M-H]^-$; Elemental Anal. Calcd for $C_{20}H_{18}N_4O_4S_3$: C, 50.62; H, 3.82; N, 11.81; S, 20.27. Found: C, 50.57; H, 4.11; N, 11.82; S, 19.99.

3.1.2. Preparation of 5-[(4-chlorophenyl)thio]-*N*-{[(2-methyl-4-phenyl-1,3-thiazol-5-yl)amino]carbonyl}thiophene-2-sulfonamide (2). To a stirred mixture of 2-methyl-4-phenyl-1,3-thiazole-5-carboxylic acid (0.150 g), 5-[(4-chlorophenyl)thio]thiophene-2-sulfonamide (0.20 g) and triethylamine (0.120 mL) in benzene (5 mL) was added diphenylphosphoryl azide (0.180 mL) under nitrogen. The mixture was then heated at 85 °C for 2 h. The cooled mixture was concentrated in vacuo and acetonitrile (3 mL), water (3 mL) and a few drops of trifluoroacetic acid were added. The resulting white solid was filtered off to give analytically pure **2** (0.220 g, 62%); mp 130–133 °C (dec); ^{1}H NMR (400 MHz, DMSO) δ 9.17 (s, 1H), 7.74 (d, $J = 3.8$ Hz, 1H), 7.66 (dm, $J = 7.4$ Hz, 2H), 7.48–7.39 (m, 7H), 7.36–7.31 (m, 1H), 2.59 (s, 3H); one NH resonance absent; ^{13}C NMR (100.5 MHz, DMSO) δ 158.9, 149.9, 142.5, 140.9, 140.8, 134.2, 133.6, 133.6, 133.5, 133.0, 131.5, 131.5, 129.7, 128.5, 127.9, 127.6, 18.7; LRMS (ESI) m/z 522, 524 $[M+H]^+$, 520, 522 $[M-H]^-$; Elemental Anal. Calcd for $C_{21}H_{16}N_3O_3S_4Cl$. H_2O: C, 46.70; H, 3.36; N, 7.78; S, 23.74. Found: C, 47.04; H, 3.43; N, 8.07; S, 23.51.

3.1.3. Preparation of *N*-(anilinocarbonyl)-4-methoxybenzenesulfonamide (8). To a stirred mixture of benzoic acid (0.122 g), 4-methoxybenzenesulfonamide (0.187 g)

and *N*,*N*-diisopropylethylamine (0.350 mL) in benzene (4 mL) was added diphenylphosphoryl azide (0.260 mL) under nitrogen. The mixture was then heated at 85 °C for 2 h. The cooled mixture was concentrated in vacuo and the residue was subjected to flash column chromatography (SiO_2, 10% to 25% ethyl acetate in isohexane) then to reverse phase HPLC (SunFire®, 5% to 90% acetonitrile in 0.1% v/v aqueous trifluoroacetic acid). The appropriate fractions were concentrated in vacuo to leave a colourless gum. This was triturated with diethyl ether to give **8** (0.132 g, 43%) as a white solid; mp 154–157 °C; ^{1}H NMR (400 MHz, DMSO) δ 10.57 (s, 1H), 8.76 (s, 1H), 7.90 (d, $J = 9.6$ Hz, 2H), 7.32 (d, $J = 8.7$ Hz, 2H), 7.25 (dd, $J = 8.9$, 7.5 Hz, 2H), 7.14 (d, $J = 9.4$ Hz, 2H), 7.01 (t, $J = 7.5$ Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (100.5 MHz, DMSO) δ 162.9, 149.4, 138.1, 131.4, 129.8, 128.9, 123.2, 118.9, 114.2, 55.7; LRMS (APCI) *m*/*z* 307 $[M+H]^+$, 305 $[M-H]^-$; Elemental Anal. Calcd for $C_{14}H_{14}N_2O_4S.1/2H_2O$: C, 53.32; H, 4.79; N, 8.88; S, 10.17. Found: C, 53.23; H, 4.46; N, 9.37; S, 10.66.

3.1.4. Preparation of 4-chloro-*N*-({[2-(dimethylamino)-4-phenyl-1,3-thiazol-5-yl]amino}carbonyl)benzenesulfonamide (24). To a stirred mixture of N^2,N^2-dimethyl-4-phenyl-1,3-thiazole-2,5-diamine (1.00 g), 4-chlorobenzene-sulfonamide (0.924 g) and *N*,*N*-diisopropylethylamine (0.80 mL) in benzene (50 mL) was added diphenylphosphoryl azide (1.05 mL) under nitrogen. The mixture was then heated at 85 °C for 2 h. The cooled mixture was diluted with ethyl acetate (200 mL) and washed with saturated aqueous sodium hydrogen carbonate (100 mL). The organic phase was dried over sodium sulfate, filtered and concentrated in vacuo. The residue was subjected to flash column chromatography (SiO_2, 5% triethylamine in ethyl acetate, then acetonitrile) then reverse phase HPLC (XTerra®, 5% to 95% acetonitrile in 0.1% v/v aqueous trifluoroacetic acid). The appropriate fractions were concentrated in vacuo to give **24** (0.580 g, 27%) as a white solid; mp 120–125 °C (dec); ^{1}H NMR (400 MHz, DMSO) δ 8.89 (s, 1H), 7.93 (dm, $J = 8.5$ Hz, 2H), 7.71 (dm, $J = 8.5$ Hz, 2H), 7.62 (dm, $J = 8.1$ Hz, 2H), 7.41–7.29 (m, 3H), 3.04 (s, 6H); one NH resonance absent; ^{13}C NMR (125.7 MHz, DMSO) δ 165.6, 158.9, 158.6, 151.0, 139.2, 134.1, 129.9, 129.8, 128.8, 128.1, 117.2, 114.8, 39.9; LRMS (APCI) *m*/*z* 437, 439 $[M+H]^+$; Elemental Anal. Calcd for $C_{18}H_{17}N_4O_3S_2Cl{\cdot}C_2HO_2F_3{\cdot}1/2H_2O$: C, 42.90; H, 3.42; N, 10.01; S, 11.45. Found: C, 42.88; H, 3.18; N, 10.11; S, 11.88.

3.2. The synthesis of sulfonylureas using a typical potassium carbonate–dioxane procedure

3.2.1. Preparation of *N*-{[(4-methoxyphenyl)amino]carbonyl}-methanesulfonamide (12). To a stirred solution of 4-methoxybenzoic acid (0.152 g) and methanesulfonamide (0.095 g) in 1,4-dioxane (4 mL) was added diphenylphosphoryl azide (0.26 mL) and potassium carbonate (0.41 g) under nitrogen. The reaction mixture was then heated at 85 °C for 2 h. The cooled mixture was concentrated in vacuo. Water was added to dissolve the solid material and the pH adjusted to 4–5 with a few drops of concentrated HCl. The solid was then collected by vacuum filtration and triturated with diethyl ether to yield **12** (0.139 g, 51%) as a white solid; mp 176–180 °C (dec); ^{1}H NMR (300 MHz, DMSO) δ 10.17 (s, 1H), 8.72 (s, 1H), 7.32 (dm, $J = 9.2$ Hz, 2H), 6.89 (dm, $J = 9.2$ Hz, 2H), 3.72 (s, 3H), 3.28 (s, 3H); ^{13}C NMR (100.5 MHz, DMSO) δ 155.3, 150.1, 130.9, 120.8, 113.9, 55.1, 41.3; LRMS (ESI) *m*/*z* 245 $[M+H]^+$, 243 $[M-H]^-$; Elemental Anal. Calcd for $C_9H_{12}N_2O_4S{\cdot}1/10(C_2\ H_5)_2O$: C, 44.86; H, 5.21; N, 11.13; S 12.74. Found: C, 44.85; H, 4.99; N, 10.96; S 12.52.

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