One-Pot Synthesis of Arylsulfonamides and Azetidine-2,4-diones via Multicomponent Reaction of an Amine, an Acetylenic Compound, and an Arylsulfonyl Isocyanate

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Abstract: An effective route to novel arylsulfonamides is described. It involves the reaction of an enamine derived from the addition of primary or secondary amines to acetylenecarboxylates (dialkyl acetylenedicarboxylates or alkyl propiolates) with an arylsulfonyl isocyanate. These arylsulfonamides show dynamic NMR behavior in solution. A different reactivity pattern was observed with the methyl 3-(diethylamino)acrylate. The latter, generated in situ from Et_2NH and methyl propiolate, on reaction with an arylsulfonyl isocyanate afforded exclusively the azetidine-2,4-dione (malonimide) derivatives in good yield. These malonimides also show dynamic NMR behavior in solution because of restricted rotation around the C–N bond resulting from conjugation of the side-chain N-atom with the adjacent α,β-unsaturated carbonyl group.

Key words: amine, alkyl propiolate, enamine, isocyanate, malonimide, arylsulfonamide, multicomponent reaction

The importance of the sulfonamide group is well established in pharmaceutical chemistry. A considerable number of sulfonamides are well known as antibacterial,[1] carbonic anhydrase inhibitor,[2] anticancer,[3] and anti-inflammatory agents.[4]

Enaminones are widely used building blocks for the synthesis of various organic compounds,[5] especially for natural bioactive substances and their analogues.[6] The enamine is one of the most important intermediates for C–C bond formation in both organic chemistry and the biological world. In organic synthesis, pyrrolidine derivatives are used to efficiently form enamines with carbonyl compounds in many reactions.

Azetidine-2,4-diones, which are highly strained molecules, have been shown to possess anti-inflammatory and sedative properties.[7] Bachi and co-workers have reported[8] that these compounds along with their 4-thioxo analogues can serve as useful intermediates for a variety of β-lactam antibiotics.[9] The structurally related monothio- and dithiophthalimides have also received attention due to their synthetic potential in photochemical studies.[10–12] Azetidinediones are employed as promoters in polymerizations and their use not only permits low polymerization temperatures, but gives rise to faster polymerization reactions than other procedures allow. The rapid polymerization of caprolactam in accordance with the present invention makes the process particularly suited to procedures for preparing molded polyamides. Azetidine-2,4-diones, that is, imides of malonic acid, are a rather little known class of heterocycles and following their first synthesis by Staudinger,[13] they have been formed in a variety of ways.[14–19]

In the context of our ongoing studies on heterocyclic synthesis mediated by enamine intermediates, the possibility of trapping the 1:1 intermediate **5**, formed between an acetylenecarboxylate **2** and a primary or secondary amine **1**, with an arysulfonyl isocyanate **3** appeared attractive from the viewpoint of devising a novel multicomponent reaction (MCR). Although the trapping of the 1:1 intermediate formed between dibenzoylacetylene or dialkyl acetylenedicarboxylate and amines with arylsulfonyl isocyanate has been studied in detail by our research group,[20–22] trapping of the initially formed 1:1 intermediate between primary amines and alkyl propiolates has not been reported.

Herein, we report a simple one-pot reaction between enamines, derived from the addition of primary or secondary amines to an acetylenic compound (dialkyl acetylenedicarboxylate or alkyl propiolate) and an arylsulfonyl isocyanate leading to the corresponding arylsulfonamides **4** (Table 1). As far as we are aware, the present synthesis represents a new method. We explored the use of Et_2NH and methyl propiolate in this reaction, which led to formation of the corresponding 1-(arylsulfonyl)-3-[(diethylamino)methylene]-2,4-azetidinedione derivatives **7**.

The reaction of amines **1**, acetylenecarboxylates **2**, and arylsulfonyl isocyanates **3** proceeded via a smooth 1:1:1 addition in anhydrous toluene at ambient temperature, to produce arylsulfonamide derivatives **4** in 80–90% yields (Table 1).

Compounds **4** apparently result from the initial addition of an amine to the acetylenic system and subsequent attack of the resulting reactive enamine **5** on the arylsulfonyl isocyanate[20–24] to yield a betaine **6**, which under hydrogen shift produce **4** (Scheme 1).

The structures of compounds **4a–g** were deduced from elemental analyses, IR, ^1H, and ^{13}C NMR spectra. No products other than **4** could be detected. The mass spectrum of **4a** displayed the molecular ion peak at *m/z* 324, which is consistent with the structure of methyl (*E*)-3-(1-azetanyl)-2-{[(phenylsulfonyl)amino]carbonyl]prop-2-enoate. The

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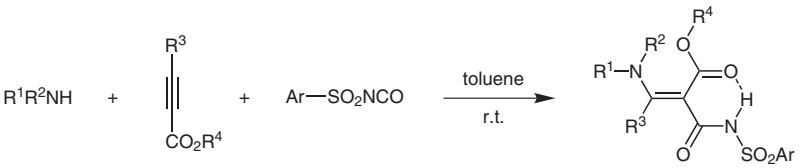
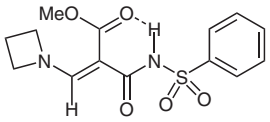
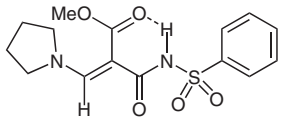
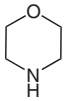
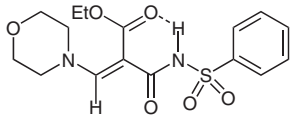
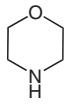
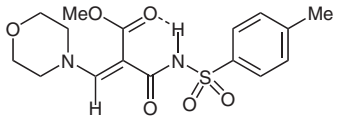
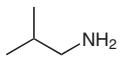
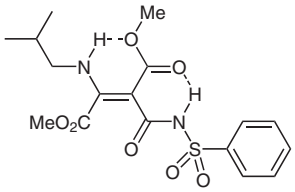
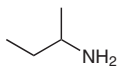
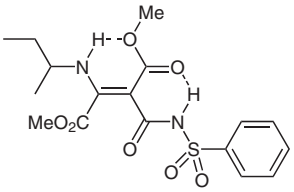
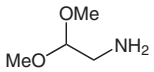
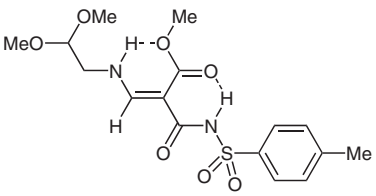
Table 1 Arylsulfonamides **4** Prepared by MCR

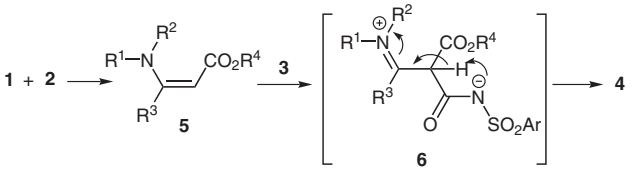


1 2 3 4

Amine **1**	Propargylic ester **2**		$ArSO_2NCO$ **3**	Product		Yield (%)[a]
	R^3	R^4	Ar			
	H	Me	Ph	**4a**		85
	H	Me	Ph	**4b**		80
	H	Et	Ph	**4c**		90
	H	Me	4-MeC_6H_4	**4d**		85
	Me	Me	Ph	**4e**		90
	Me	Me	Ph	**4f**		90
	H	Me	4-MeC_6H_4	**4g**		90

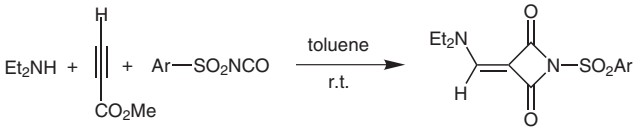
[a] Yields of isolated products.

IR spectrum of **4a** exhibited the absorption bands for the carbonyl groups of ester and amide at 1672 and 1644 cm^{-1}, respectively, for the conjugated C=C bond at 1583 cm^{-1}, and for the sulfonyl moiety at about 1336 and 1166 cm^{-1}. The ^1H NMR spectrum of **4a** exhibited six signals readily recognized as arising from three CH_2 groups [δ = 2.29 (m), 4.25 (t, $^3J_{H,H}$ = 7.8 Hz), and 4.41 (m)], a CH_3O (δ = 3.70), a vinylic CH (δ = 7.63), and an NH (δ = 11.6) proton. The Ph moiety gave rise to characteristic signals in the aromatic region of the spectrum. The ^1H-decoupled ^{13}C NMR spectrum of **4a** showed 12 distinct resonances in agreement with the proposed structure. Partial assignment of these resonances is given in the experimental section. The ^1H and ^{13}C NMR spectra of compounds **4b–g** are



Scheme 1

Table 2 Compounds **7** Prepared



7	Ar	Yield (%)
a	Ph	90
b	4-MeC_6H_4	90

similar to those of **4a**, except for the amine moiety, which exhibits characteristic signals with the appropriate chemical shifts (see experimental section).

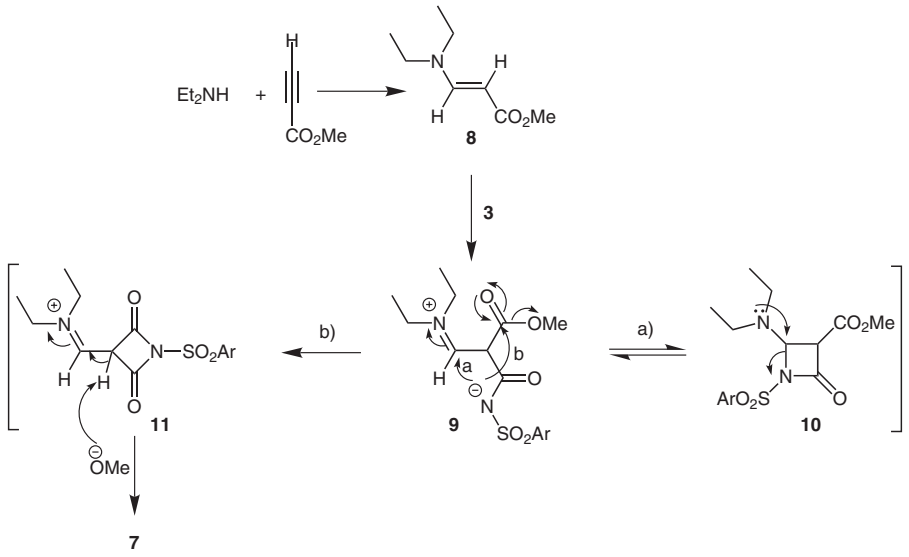
In view of the success of the above reaction (Table 1), we explored the use of Et_2NH, which has shown a different reactivity in this reaction. Treatment of Et_2NH with methyl propiolate (**2a**) in the presence of **3** in anhydrous toluene at room temperature gave 1-(arylsulfonyl)-3-[(diethylamino)methylene]-2,4-azetidinedione derivatives **7** in 90% yield (Table 2).

Although we have not established the mechanism of the reaction of the enamine derived from the addition of Et_2NH to **2a** and **3** in an experimental manner, a possible explanation is proposed in Scheme 2. Compound **7** apparently results from the initial addition of Et_2NH to the acetylenic system and subsequent attack of the resulting reactive enamine **8** to the arylsufonyl isocyanate[20–24] to yield betaine **9**, which apparently cyclizes, under the reaction condition employed with loss of methanol to produce the malonimide **7**.

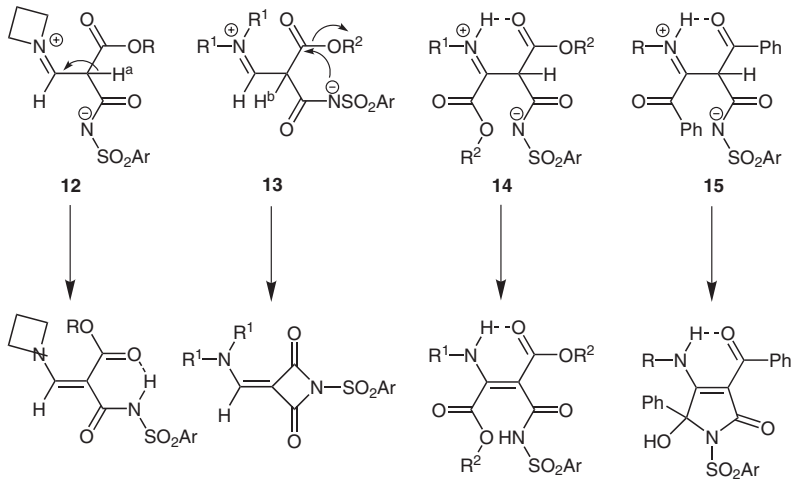
We have unraveled some interesting reactivity profiles of the intermediates **12**, **13**, **14**, and **15**.[20–22] Intermediate **12** undergoes a proton transfer but intermediate **13** undergoes cyclization leading to the corresponding products. This is because, H^a in intermediate **12** is more acidic than H^b in intermediate **13**. Also in intermediate **15** carbonyl group of COPh is more electrophilic than the carbonyl group of CO_2R in intermediate **14** (Scheme 3).

In summary, the reaction between Et_2NH, methyl propiolate (**2a**) and an arylsulfonyl isocyanate **3** provides a simple one-pot synthesis of 3-[(diethylamino)methylene]-1-(arylsulfonyl)-2,4-azetidinedione derivatives **7** of potential synthetic and pharmaceutical interest. With other amines, the reaction leads to the formation of the corresponding arylsulfonamides. The present method has the advantage that it can be performed under neutral conditions and requires no activation or modification of the starting materials. The simplicity of the present procedure makes it an interesting alternative to complex multistep approaches.[19]

Methyl and ethyl acetylenecarboxylates, benzenesulfonyl isocyanate, and tosyl isocyanate, were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. ^1H, and ^{13}C NMR, spectra were measured ($CDCl_3$ solution) with a Bruker DRX-500 Avance spectrometer at 500.1 and 125.7 MHz, respectively. IR spectra were recorded on a Shimadzu IR-460 spectrometer.



Scheme 2



Scheme 3

Methyl (*E*)-3-(1-Azetanyl)-2-{[(phenylsulfonyl)amino]carbonyl}prop-2-enoate (4a); Typical Procedure

A solution of methyl propiolate (**2a**; 0.084 g, 1 mmol) and azetan (**1a**; 0.057 g, 1 mmol) in anhyd toluene (5 mL) was magnetically stirred for 5 h. To this solution was added dropwise a solution of phenylsulfonyl isocyanate (0.18 g, 1 mmol) in anhyd toluene (3 mL) at 25 °C and the mixture was stirred for 12 h. The solvent was removed under reduced pressure, and the residue was separated by silica gel (Merck 230–240 mesh) column chromatography using hexane–EtOAc (5:1) as eluent; yield: 0.27 g (85%); yellow liquid.

IR (KBr): 3400 (NH), 1672 (CO_2Me), 1644 (NCO), 1583 (NC=C), 1500 and 1433 (Ar), 1336 and 1166 (SO_2), 1120 and 1078 cm^{-1} (C–O).

^1H NMR (300.1 MHz, $CDCl_3$): δ = 2.29 (2 H, m, CH_2), 3.70 (3 H, s, OCH_3), 4.25 (2 H, t, $^3J_{H,H}$ = 7.8 Hz, CH_2N), 4.41 (2 H, m, CH_2N), 7.47 (2 H, t, $^3J_{H,H}$ = 7.7 Hz, 2 CH_{meta} of Ph), 7.52 (1 H, t, $^3J_{H,H}$ = 7.2 Hz, CH_{para} of Ph), 7.63 (1 H, s, NCH=C), 8.04 (2 H, t, $^3J_{H,H}$ = 7.4 Hz, 2 CH_{ortho} of Ph), 11.60 (1 H, s, NH).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 22.93 (CH_2), 57.62 (CH_2N), 58.71 (CH_2N), 68.09 (OCH_3), 88.60 (NCH=*C*), 125.72 (2 CH_{meta} of Ph), 126.28 (CH_{para} of Ph), 128.75 (2 CH_{ortho} of Ph), 130.88 (C_{ipso} of Ph), 156.58 (N*C*H=C), 167.50 (CON), 169.50 (*C*O_2Me).

MS: *m*/*z* (%) = 324 (M^+, 1), 287 (2), 257 (1), 229 (5), 183 (9), 167 (8), 141 (31), 110 (12), 94 (10), 77 (100), 56 (20), 51 (40), 41 (18).

Anal. Calcd for $C_{14}H_{16}N_2O_5S$ (324.35): C, 51.84; H, 4.97; N, 8.64. Found: C, 51.66; H, 4.87; N, 8.76.

Methyl (*E*)-2-{[(Phenylsulfonyl)amino]carbonyl}-3-(1-pyrrolidinyl)prop-2-enoate (4b)

Yield: 0.27 g (80%); white powder; mp 145–147 °C.

IR (KBr): 3400 (NH), 1670 (CO_2Me), 1635 (NCO), 1580 (NC=C), 1507 and 1418 (Ar), 1335 and 1177 (SO_2), 1106 and 1040 cm^{-1} (C–O).

^1H NMR (300.1 MHz, $CDCl_3$): δ = 1.88 (4 H, s, 2 CH_2 of pyrrolidine), 3.27 (2 H, s, CH_2N of pyrrolidine), 3.62 (2 H, s, CH_2N of pyrrolidine), 3.69 (3 H, s, OCH_3), 7.44 (2 H, t, $^3J_{H,H}$ = 7.5 Hz, 2 CH of Ph), 7.52 (1 H, t, $^3J_{H,H}$ = 6.9 Hz, CH of Ph), 8.02 (2 H, t, $^3J_{H,H}$ = 7.3 Hz, 2 CH of Ph), 8.03 (NCH=C), 11.45 (1 H, s, NH).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 24.05 (CH_2 of pyrrolidine), 25.61 (CH_2 of pyrrolidine), 51.42 (CH_2N), 52.93 (CH_2N), 56.25 (OCH_3), 89.23 (NCH=*C*), 127.94 (2 CH_{meta} of Ph), 128.67 (2 CH_{ortho} of Ph), 133.06 (CH_{para} of Ph), 139.94 (C_{ipso} of Ph), 156.63 (N*C*H=C), 162.55 (NCO), 168.80 (*C*O_2Me).

MS: *m*/*z* (%) = 197 (4), 183 (13), 181 (3), 165 (13), 140 (31), 124 (24), 106 (7), 96 (13), 77 (100), 68 (10), 51 (46), 41 (28).

Anal. Calcd for $C_{15}H_{18}N_2O_5S$ (338.37): C, 53.24; H, 5.36; N, 8.28. Found: C, 53.63; H, 5.45; N, 8.14.

Ethyl (*E*)-3-Morpholino-2-{[(phenylsulfonyl)amino]carbonyl}prop-2-enoate (4c)

Yield: 0.33 g (90%); white powder; mp 172–174 °C.

IR (KBr): 3195 (NH), 1682 (CO_2Me), 1640 (NCO), 1573 (NC=C), 1500 and 1455 (Ar), 1324 and 1156 (SO_2), 1112 and 1082 cm^{-1} (C–O).

^1H NMR (500.1 MHz, MeOH-d_4): δ = 1.24 (3 H, t, $^3J_{H,H}$ = 7.2 Hz, OCH_2CH_3), 3.37 (4 H, t, $^3J_{H,H}$ = 4.7 Hz CH_2NCH_2), 3.59 (4 H, t, $^3J_{H,H}$ = 4.7 Hz, CH_2OCH_2), 4.07 (1 H, t, $^3J_{H,H}$ = 7.07 Hz, CH_2CH_3), 4.17 (1 H, t, $^3J_{H,H}$ = 7.0 Hz, CH_2CH_3), 7.54 (2 H, t, $^3J_{H,H}$ = 7.4 Hz, 2 CH of Ph), 7.63 (2 H, t, $^3J_{H,H}$ = 7.5 Hz, CH of Ph), 7.85 (1 H, s, NH), 7.98 (NCH=C), 7.99 (1 H, d, $^3J_{H,H}$ = 7.2 Hz, 2 CH of Ph).

^{13}C NMR (125.7 MHz, MeOH-d_4): δ = 14.84 (CH_3CH_2), 43.69 (CH_2N), 44.23 (CH_2N), 63.84 (CH_2O), 66.57 (2 CH_2O), 110.00 (NCH=*C*), 126.51 (2 CH_{meta} of Ph), 128.57 (2 CH_{ortho} of Ph), 128.86 (CH_{para} of Ph), 139.63 (C_{ipso} of Ph), 142.10 (N*C*H=C), 153.07 (CON), 156.00 (*C*O_2Me).

MS: *m*/*z* (%) = 183 (17), 156 (16), 141 (33), 138 (7), 112 (10), 98 (4), 94 (5), 77 (100), 57 (12), 51 (39), 41 (10).

Anal. Calcd for $C_{16}H_{20}N_2O_6S$ (368.40): C, 52.16; H, 5.47; N, 7.60. Found: C, 52.31; H, 5.43; N, 7.54.

Methyl (*E*)-2-({[(4-Methylphenyl)sulfonyl]amino}carbonyl)-3-morpholinoprop-2-enoate (4d)

Yield: 0.31 g (85%); white powder; mp 90–92 °C.

IR (KBr): 3430 (NH), 1668 (CO_2Me), 1644 (NCO), 1576 (NC=C), 1507 and 1422 (Ar), 1332 and 1161 (SO_2), 1116 and 1071 cm^{-1} (C–O).

^1H NMR (500.1 MHz, $CDCl_3$): δ = 2.41 (3 H, s, CH_3), 3.51 (4 H, br, 2 CH_2N), 3.75 (4 H, s, 2 CH_2O), 3.80 (3 H, s, OCH_3), 7.29 (2 H, d, $^3J_{H,H}$ = 8.1 Hz, 2 CH of Ar), 7.92 (1 H, s, NCH=C), 7.96 (2 H, d, $^3J_{H,H}$ = 8.2 Hz, 2 CH of Ar), 11.41 (1 H, s, NH).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 21.49 (Ar*C*H_3), 51.61 (OCH_3), 52.27 (NCH_2), 55.98 (NCH_2), 66.62 (2 CH_2O), 88.68 (NCH=*C*), 128.19 (2 CH of Ar), 129.31 (2 CH of Ar), 137.18 (C_{ipso}-SO_2 of Ar), 143.97 (C_{ipso}-CH_3 of Ar), 159.16 (N*C*H=C), 162.82 (NCO), 168.71 (*C*O_2Me).

MS: *m*/*z* (%) = 369 (M^+ + 1, 0.3), 268 (1), 262 (0.3), 213 (1), 197 (34), 171 (24), 155 (58), 140 (30), 112 (29), 91 (100), 82 (24), 65 (30), 42 (17), 41 (17).

Anal. Calcd for $C_{16}H_{20}N_2O_6S$ (368.40): C, 52.16; H, 5.47; N, 7.60. Found: C, 52.23; H, 5.53; N, 7.42.

Dimethyl (*E*)-2-(Isobutylamino)-3-{[(phenylsulfonyl)amino]carbonyl}but-2-enedioate (4e)
Yield: 0.36 g (90%); white powder; mp 95–97 °C.

IR (KBr): 3335 (NH), 3140 (NH), 1742 (CO_2Me), 1659 (NCO), 1634 (NC=C) 1575 and 1427 (Ar), 1331 and 1174 (SO_2), 1231 and 1134 cm^{-1} (C–O).

^1H NMR (500.1 MHz, $CDCl_3$): δ = 0.92 (6 H, d, $^3J_{H,H}$ = 6.7 Hz, 2 CH_3), 1.85 (1 H, m, CH), 2.98 (2 H, t, $^3J_{H,H}$ = 6.6 Hz, CH_2), 3.72 (3 H, s, OCH_3), 3.89 (3 H, s, OCH_3), 7.53 (2 H, t, $^3J_{H,H}$ = 7.9 Hz, 2 CH of Ph), 7.62 (1 H, t, $^3J_{H,H}$ = 7.4Hz, CH of Ph), 8.08 (2 H, d, $^3J_{H,H}$ = 8.7 Hz, 2 CH of Ph), 11.36 (1 H, s, N*H*CH_2), 11.78 (1 H, s, CONH).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 19.85 (2 CH_3), 28.86 (CH), 52.19 (OCH_3), 52.87 (OCH_3), 53.82 (CH_2), 86.29 (NC=*C*), 128.21 (2 CH_{meta} of Ph), 128.75 (2 CH_{ortho} of Ph), 133.35 (CH_{para} of Ph), 139.74 (C_{ipso} of Ph), 162.61 (N*C*=C), 162.68 (CON), 167.27 (*C*O_2Me), 167.35 (*C*O_2Me).

MS: *m*/*z* (%) = 398 (M^+, 7), 367 (4), 323 (12), 302 (4), 291 (7), 270 (3) 257 (2), 242 (8), 225 (20), 215 (7), 208 (6), 193 (39), 172 (8), 160 (8), 141 (32), 140 (20), 126 (20), 100 (4), 94 (15), 77 (100), 57 (26), 51 (23), 41 (26).

Anal. Calcd for $C_{17}H_{22}N_2O_7S$ (398.42): C, 51.25; H, 5.57; N, 7.03. Found: C, 51.75; H, 5.36; N, 7.16.

Dimethyl (*E*)-2-(*sec*-Butylamino)-3-{[(phenylsulfonyl)amino]carbonyl}but-2-enedioate (4f)
Yield: 0.36 g (90%); white powder; mp 115–117 °C.

IR (KBr): 3415 (NH), 3125 (NH), 1743 (CO_2Me), 1670 (NCO), 1610 (NC=C), 1571 and 1427 (Ar), 1343 and 1132 (SO_2), 1105 and 1080 cm^{-1} (C–O).

^1H NMR (300.1 MHz, $CDCl_3$): δ = 0.87 (3 H, t, $^3J_{H,H}$ = 7.4 Hz, CH_2CH_3), 1.21 (3 H, d, $^3J_{H,H}$ = 6.4 Hz, $CHCH_3$), 1.55 (2 H, m, CH_2CH_3), 3.17 (1 H, m, NCH), 3.72 (3 H, s, OCH_3), 3.89 (3 H, s, OCH_3), 7.54 (2 H, t, $^3J_{H,H}$ = 7.7 Hz, 2 CH of Ph), 7.62 (1 H, t, $^3J_{H,H}$ = 7.2 Hz, CH_{para} of Ph), 8.08 (2 H, t, $^3J_{H,H}$ = 7.4 Hz, 2 CH of Ph), 11.22 (1 H, d, $^3J_{H,H}$ = 4.0 Hz, N*H*CH), 11.82 (1 H, s, NH).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 10.03 ($CHCH_3$), 21.45 (CH_2CH_3), 30.11 (CH_2CH_3), 52.19 (OCH_3), 52.86 (OCH_3), 55.52 (*C*HNH), 85.67 (NC=*C*), 128.12 (2 CH of Ph), 128.77 (2 CH of Ph), 133.31 (CH of Ph), 139.73 (C_{ipso} of Ph), 161.62 (N*C*=C), 162.70 (CONH), 167.29 (*C*O_2Me), 167.33 (*C*O_2Me).

MS: *m*/*z* (%) = 398 (7), 366 (3), 333 (9), 337 (18), 305 (10), 240 (11) 225 (16), 193 (40), 180 (11), 141 (40), 126 (30), 94 (13), 77 (100), 59 (20), 51 (24), 41 (48).

Anal. Calcd for $C_{17}H_{22}N_2O_7S$ (398.42): C, 51.25; H, 5.57; N, 7.03. Found: C, 51.17; H, 5.36; N, 7.24.

Methyl (*E*)-[(2,2-Dimethoxyethyl)amino]-2-({[(4-methylphenyl)sulfonyl]amino}carbonyl)prop-2-enoate (4g)
Yield: 0.35 g (90%); white powder; mp 80–82 °C.

IR (KBr): 3275 (NH), 1669 (C=O), 1596 and 1432 (Ar), 1321 and 1160 (SO_2), 1111 and 1073 cm^{-1} (C–O).

^1H NMR (300.1 MHz, $CDCl_3$): δ = 2.42 (3 H, s, CH_3), 3.34–3.37 (2 H, m, CH_2), 3.39 (6 H, s, 2 OCH_3), 3.74 (3 H, s, OCH_3), 4.35 (1 H, t, $^3J_{H,H}$ = 5.08 Hz, CH), 7.31 (2 H, d, $^3J_{H,H}$ = 8.1 Hz, 2 CH of Ar), 7.91 (CH=C), 7.96 (2 H, d, $^3J_{H,H}$ = 8.2 Hz, 2 CH of Ar), 9.91 (1 H, t, $^3J_{H,H}$ = 5.9 Hz, N*H*CH_2), 11.62 (1 H, s, NHCO).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 21.65 (ArCH_3), 51.64 (NCH_2), 51.82 (OCH_3), 55.00 (2 OCH_3), 89.18 (CH=*C*), 102.72 (CH), 128.12 (2 CH of Ar), 129.38 (2 CH of Ar), 137.05 (C_{ipso}-SO_2 of Ar), 144.14 (C_{ipso}-CH_3 of Ar), 160.99 (H*C*=C), 166.35 (CONH), 168.44 (*C*O_2Me).

MS: *m*/*z* (%) = 386 (M^+, 1), 355 (0.3), 326 (1), 279 (0.3), 231 (0.5). 215 (0.5), 199 (0.5), 186 (3), 171 (2), 155 (1), 139 (1), 123 (1), 108 (1), 91 (11), 75 (100), 65 (4), 47 (7), 41 (1).

Anal. Calcd for $C_{16}H_{22}N_2O_7S$ (386.42): C, 49.73; H, 5.74; N, 7.25. Found: C, 49.87; H, 5.69; N, 7.13.

3-[(Diethylamino)methylene]-1-(phenylsulfonyl)-2,4-azetidinedione (7a)
Yield: 0.27 g (90%); colorless crystals; mp 62–64 °C.

IR (KBr): 1723 (CONCO), 1606 (NC=C), 1443 (Ar), 1349 and 1076 cm^{-1} (SO_2).

^1H NMR (300.1 MHz, $CDCl_3$): δ = 1.13 (3 H, t, $^3J_{H,H}$ = 7.2 Hz, CH_2CH_3), 1.24 (3 H, t, $^3J_{H,H}$ = 7.2 Hz, CH_2CH_3), 3.37 (2 H, q, $^3J_{H,H}$ = 7.2 Hz, CH_2CH_3), 3.46 (2 H, q, $^3J_{H,H}$ = 7.2 Hz, CH_2CH_3), 7.41–7.55 (3 H, m, Ph), 7.87 (2 H, dd, $^3J_{H,H}$ = 8.0 Hz, $^4J_{H,H}$ = 1.8 Hz, 2 CH_{ortho} of Ph), 8.14 (1 H, s, CH).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 12.04 (CH_2CH_3), 14.45 (CH_2CH_3), 40.94 (CH_2CH_3), 47.08 (CH_2CH_3), 126.27 (C-3 of azetidine ring), 126.30 (2 CH of Ph), 128.64 (2 CH of Ph), 131.69 (CH of Ph), 142.55 (C_{ipso} of Ph), 158.14 (2 C=O of azetidine ring and CH).

MS: *m*/*z* (%) = 221 (3), 167 (14), 149 (35), 113 (5), 99 (38), 94 (9), 77 (58), 57 (42), 41 (40).

Anal. Calcd for $C_{14}H_{16}N_2O_4S$ (308.35): C, 54.53; H, 5.23; N, 9.08. Found: C, 55.00; H, 5.52; N, 9.00.

3-[(Diethylamino)methylene]-1-[(4-methylphenyl)sulfonyl]-2,4-azetidinedione (7b)
Yield: 0.28 g (90%); colorless crystals; mp 52–54 °C.

IR (KBr): 1733 (CONCO), 1603 (NC=C), 1500 and 1442 (Ar), 1345 and 1141 cm^{-1} (SO_2).

^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.12 (3 H, t, $^3J_{H,H}$ = 7.2 Hz, CH_2CH_3), 1.23 (3 H, t, $^3J_{H,H}$ = 7.2 Hz, CH_2CH_3), 2.37 (3 H, s, CH_3), 3.36 (2 H, q, $^3J_{H,H}$ = 7.2 Hz, CH_2CH_3), 3.45 (2 H, q, $^3J_{H,H}$ = 7.2 Hz, CH_2CH_3), 7.24 (2 H, d, $^3J_{H,H}$ = 8.1 Hz, 2 CH of Ar), 7.74 (2 H, d, $^3J_{H,H}$ = 8.1 Hz, 2 CH of Ar), 8.13 (1 H, s, CH).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 12.08 (CH_2CH_3), 14.49 (CH_2CH_3), 21.45 (ArCH_3), 40.94 (NCH_2CH_3), 47.08 (NCH_2CH_3), 126.30 (C-3 of azetidine ring), 126.35 (2 CH of Ar), 129.30 (2 CH of Ar), 139.85 (C_{ipso}-SO_2 of Ar), 142.29 (C_{ipso}-CH_3 of Ar), 158.14 (2 C=O of azetidine ring and CH).

MS: *m*/*z* (%) = 254 (6), 226 (4), 213 (5), 207 (10), 194 (3), 175 (9), 155 (41), 153 (7), 126 (7), 123 (9), 108 (53), 91 (100), 72 (25), 65 (43), 44 (56).

Anal. Calcd for $C_{15}H_{18}N_2O_4S$ (322.38): C, 55.80; H, 5.63; N, 8.69. Found: C, 56.00; H, 5.70; N, 8.70.

References

(1) (a) Joshi, S.; Khosla, N. *Bioorg. Med. Chem. Lett.* **2003**, *52*, 197. (b) Joshi, S.; Khosla, N.; Tiwari, P. *Bioorg. Med. Chem.* **2004**, *12*, 571.
(2) Supuran, C. T.; Scozzafava, A.; Casini, A. *Med. Res. Rev.* **2003**, *23*, 146.

(3) Scozzafava, A.; Owa, T.; Mastrolorenzo, A.; Supuran, C. T. *Curr. Med. Chem.* **2003**, *10*, 925.
(4) Weber, A.; Casini, A.; Heine, A.; Kuhn, D.; Supuran, C. T.; Scozzafava, A.; Kiebe, G. *J. Med. Chem.* **2004**, *47*, 550.
(5) Kukländer, U. *Enamines as Synthones,* In *The Chemistry of Enamines*; Rappaport, Z., Ed.; Wiley: Chichester, **1994**, 523.
(6) Michael, J. P.; de Konig, C. B.; Gravestock, D.; Hosken, G. D.; Howard, A. S.; Jungmann, C. M.; Krause, R. W. M.; Parsons, A. S.; Pelly, S. C.; Stanbury, T. V. *Pure Appl. Chem.* **1999**, *71*, 979.
(7) Moore, J. A. In *Heterocyclic Compounds with Three and Four Membered Rings*, Part 2; Weissberger, A., Ed.; Wiley-Interscience: New York, **1964**, 951.
(8) (a) Bachi, M. D.; Goldberg, O.; Gross, A.; Vaya, J. *J. Org. Chem.* **1980**, *45*, 1477. (b) Chou, T. S.; Koppel, G. A.; Dorman, D. E.; Paschal, J. W. *J. Am. Chem. Soc.* **1976**, *98*, 7864.
(9) Brandt, A.; Bassignani, L.; Re, L. *Tetrahedron Lett.* **1976**, 3975.
(10) Machida, M.; Oda, K.; Yoshida, E.; Kanaoka, Y. *Tetrahedron* **1986**, *42*, 4691.
(11) Coyle, J. D.; Rapley, P. A. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2273.
(12) Sakamoto, M.; Aoyama, H.; Omote, Y. *J. Org. Chem.* **1984**, *49*, 396.
(13) Staudinger, H.; Göhring, O.; Schöller, M. *Ber. Dtsch. Chem. Ges.* **1914**, *47*, 40.
(14) Ebnöther, A.; Jucker, E.; Rissi, E.; Rutschmann, J.; Schreier, E.; Steiner, R.; Vogel, A. *Helv. Chim. Acta* **1959**, *42*, 918.
(15) Kanaoka, Y.; Okajima, H.; Hatanaka, Y. *J. Org. Chem.* **1979**, *44*, 1749.
(16) Maruyama, K.; Ishitoku, T.; Kubo, Y. *J. Am. Chem. Soc.* **1979**, *101*, 3670.
(17) Maruyama, K.; Ishitoku, T.; Kubo, Y. *J. Org. Chem.* **1981**, *46*, 27.
(18) Aoyama, H.; Sakamoto, M.; Omote, Y. *J. Chem. Soc., Chem. Commun.* **1982**, 119.
(19) Bari, S. S.; Trehan, I. R.; Sharma, A. K.; Manhas, M. S. *Synthesis* **1992**, 439.
(20) Alizadeh, A.; Movahedi, F.; Esmaili, A. A. *Tetrahedron Lett.* **2006**, *47*, 4469.
(21) Alizadeh, A.; Movahedi, F.; Masrour, H.; Zhu, L. G. *Synthesis* **2006**, 3431.
(22) Alizadeh, A.; Rezvanian, A.; Zhu, L. G. *Helv. Chim. Acta* **2007**, *90*, 2414.
(23) Gerus, I. I.; Lyutenko, N. V.; Kacharov, A. D.; Kukhar, V. P. *Tetrahedron Lett.* **2000**, *41*, 10141.
(24) Lyutenko, N. V.; Gerus, I. I.; Kacharov, A. D.; Kukhar, V. P. *Tetrahedron* **2003**, *59*, 1731.