Stereospecific Synthesis of Functionalized C5-Unsaturated Hydantoin Derivatives via a Three-Component Reaction

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Received 5 December 2007; revised 1 January 2008

Abstract: An effective route to functionalized C5-unsaturated hydantoin derivatives is described. This involves the reaction of a urea derivative, derived from the addition of a primary amine to an arylsulfonyl isocyanate, and a dialkyl acetylenedicarboxylate in the presence of isoquinoline.

Key words: primary amine, arylsulfonyl isocyanate, dialkyl acetylenedicarboxylate, hydantoin, isoquinoline, multicomponent reaction

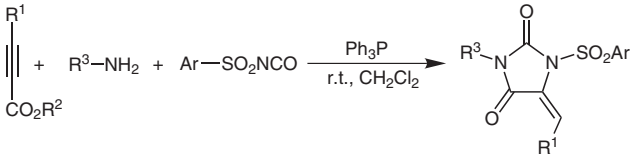
Hydantoins (imidazolidine-2,4-diones), and their bi- and tricyclic derivatives, represent an important class of biologically active molecules that have broad medical[1] (anticancer, anticonvulsant, antimuscrinic, antiulcer, and antiarrhytmic) and agrochemical[2] (herbicidal and fungicidal) application.

From the point of view of organic synthesis, hydantoins have been frequently used as precursors of unnatural α-amino acids.[3,4]

C5-Unsaturated hydantoins are important as biological and pharmacological intermediates as precursors to C5-substituted hydantoins and their subsequent α-amino acids.[5,6] Classic methods for the preparation of C5-substituted hydantoins are (i) base- and acid-catalyzed condensations of 5-unsubstituted hydantoins with aldehydes and unhindered or activated ketones[5] and (ii) reactions of aldehydes, certain ketones, and α-dicarbonyl compounds in the presence of a base with diethyl (2,5-dioxoimidazolidin-4-yl)phosphonates, which are obtained from 5-bromohydantoin, triethyl phosphite, and acetic acid.[6] Synthesis of C5 functionally substituted hydantoins, however, has been limited.[6,7]

We have recently reported a multicomponent reaction mediated by zwitterionic intermediates.[8] Treatment of a primary amine, an arylsulfonyl isocyanate, and a dialkyl acetylenedicarboxylate in the presence of triphenylphosphine in anhydrous dichloromethane at room temperature leads to the formation of alkyl (*E*)-[1-alkyl-3-(arylsulfonyl)-2,5-dioxoimidazolidin-4-ylidene]acetate derivatives (Scheme 1).[8]

In the context of our ongoing studies on heterocyclic construction mediated by zwitterionic intermediates, the possibility of trapping the 1:1 intermediate formed between dialkyl acetylenedicarboxylate and isoquinoline with a urea derivative appeared attractive from the viewpoint of devising a novel MCR. In view of the success of the above reaction, we explored the use of isoquinoline as the catalyst in this reaction. In this paper, we present the results of an extended investigation of the reactivity of the intermediate zwitterions with a urea derivative in dichloromethane. To our surprise, the products of the two reactions (Scheme 1 and Table 1) are geometrical isomers (Figure 1).



Scheme 1

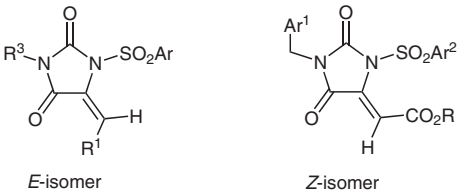


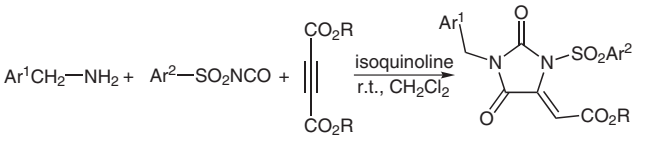
Figure 1

Herein, we wish to report a simple one-pot reaction between a urea derivative, derived from the addition of a primary amine to an arylsulfonyl isocyanate, and a dialkyl acetylenedicarboxylate in the presence of isoquinoline leading to alkyl (*E*)-[1-alkyl-3-(arylsulfonyl)-2,5-dioxoimidazolidin-4-ylidene]acetate derivatives **4**. The reaction proceeds in dichloromethane at ambient temperature, and produces hydantoin derivatives **4** in 80–90% yields (Table 1).

The structure of compounds **4a**–**g** was deduced from their elemental analysis and IR and high-field ^{1}H and ^{13}C NMR spectra. The mass spectrum of **4a** displayed a molecular ion peak at *m*/*z* = 414, which was consistent with the 1:1:1 adduct of benzyl amine, tosyl isocyanate, and dimethyl acetylenedicarboxylate minus methanol. The ^{1}H NMR spectrum of **4a** exhibited four single sharp lines readily recognized as arising from methyl (δ = 2.47), methoxy (δ = 3.87), and methylene (δ = 4.61) protons along with a vinylic CH (δ = 7.01) and phenyl moieties, which give

SYNTHESIS 2008, No. x, pp 000A–000D
Advanced online publication: xx.xx.2008
DOI: 10.1055/s-2008-1066993; Art ID: Z28107SS

Table 1 Reaction of Primary Amines **1** with Arylsulfonyl Isocyanates **2** and Dialkyl Acetylenedicarboxylates **3** in the Presence of Isoquinoline



1 2 3 4

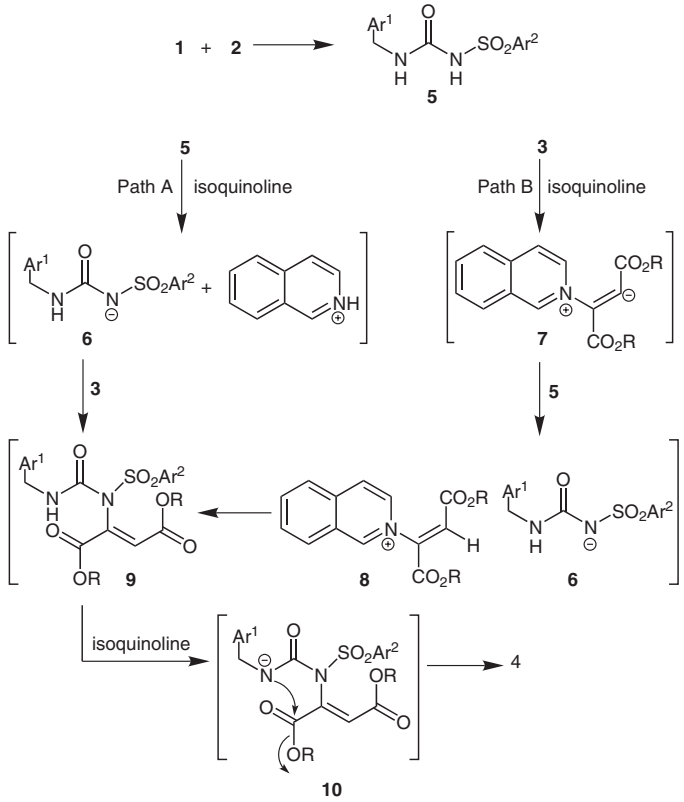
Product	Ar^1	Ar^2	R	Yield (%)
4a	Ph	4-MeC_6H_4	Me	89
4b	2-ClC_6H_4	4-MeC_6H_4	Me	85
4c	2-ClC_6H_4	Ph	Me	80
4d	Ph	4-MeC_6H_4	Et	89
4e	2-ClC_6H_4	4-MeC_6H_4	Et	90
4f	Ph	Ph	Et	85
4g	2-ClC_6H_4	Ph	Et	80

characteristic signals in the aromatic region of the spectrum. The ^1H decoupled ^{13}C NMR spectrum of **4a** showed 14 distinct resonances in agreement with the methyl (1-benzyl-2,5-dioxo-3-tosylimidazolidin-4-ylidene)acetate structure.

The ^1H and ^{13}C NMR spectra of compounds **4b–g** are similar to those of **4a**, except for the alkyl group of the esters moiety and the aromatic rings, which exhibit characteristic signals with appropriate chemical shifts and coupling constants.

Although we have not established the mechanism of the reaction between dialkyl acetylenedicarboxylates **3** and urea derivative **5**, which derived from the addition of a primary amine **1** to an arylsulfonyl isocyanate **2**, in the presence of isoquinoline in an experimental manner, a possible explanation is proposed in Scheme 2. On the basis of the well-established chemistry of the isocyanates[9–11] and isoquinoline as a nucleophile,[12–16] it is reasonable to assume that functionalized hydantoin **4** results from the deprotonation and cyclization of intermediate **9**, which can be generated by two paths A or B. At first the reaction between a primary amine and arylsulfonyl isocyanate leads to the urea derivative **5**, which is an NH-acid. Following path A, compound **5** is deprotonated by the isoquinoline and leads to intermediate **6**, which reacts with dialkyl acetylenedicarboxylate and generates intermediate **9**. Following path B, the reactive 1:1 intermediate obtained from the addition of isoquinoline to a dialkyl acetylenedicarboxylate is trapped by an NH-acid such as compound **5** to produce intermediate **8**. Then, the positively charged ion **8** might be attacked by the conjugate base of the NH-acid **6** to form intermediate **9**, which in turn is converted into intermediate **10** in the presence of isoquinoline. Cyclization of the intermediate **10** leads to compound **4** (Scheme 2).

In summary, we have found a simple, efficient, and stereospecific method for the preparation of stabilized hydantoins. The present method has the advantages that, not



Scheme 2

only is the reaction performed under neutral conditions, but the substances can be mixed without any activation or modification. The simplicity of the present procedure makes it an interesting alternative to complex multistep approaches.

Amines, arylsulfonyl isocyanates, and dialkyl acetylenedicarboxylates 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 20 eV. ^{1}H and ^{13}C NMR spectra were measured ($CDCl_3$) with a Bruker DRX-500 Avance spectrometer at 500.1 and 125.8 MHz, respectively. IR spectra were recorded on a Shimadzu IR-460 spectrophotometer. Chromatography columns were prepared from Merck silica gel 230–240 mesh.

Methyl (*Z*)-(1-Benzyl-2,5-dioxo-3-tosylimidazolidin-4-ylidene)acetate (4a); Typical Procedure

To a soln of $BnNH_2$ (0.11 g, 1 mmol) and TsNCO (0.18 g, 1 mmol) in anhyd CH_2Cl_2 (5 mL) was magnetically stirred for 30 min and then isoquinoline (0.13 g, 1 mmol) was added followed by the dropwise addition of a soln of DMAD (0.14 g, 1 mmol) in anhyd CH_2Cl_2 (3 mL) at r.t. over 10 min. The mixture was then allowed to stir for 2 h. The solvent was removed under reduced pressure, and the residue was separated by column chromatography (silica gel, Merck 230–240 mesh, hexane–EtOAc) as a white powder; yield: 0.37 g (89%); mp 149–150 °C.

IR (KBr): 1796 and 1756 (2 C=O, hydantoin), 1701 (CO_2Me), 1651 (C=C), 1555 and 1453 (Ar), 1325 and 1170 (SO_2), 1257 (C–O, ester) cm^{-1}.

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 2.47 (s, 3 H, CH_3), 3.87 (s, 3 H, OMe), 4.61 (s, 2 H, C*H*$_2$Ph), 7.01 (s, 1 H, C=C*H*), 7.29 (5 H_{arom}), 7.38 (d, $^3J_{HH}$ = 8.1 Hz, 2 H_{arom}), 7.94 (d, $^3J_{HH}$ = 8.3 Hz, 2 H_{arom}).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 21.78 (CH_3), 43.10 (*C*H$_2$Ph), 52.82 (OMe), 111.38 (C=*C*H), 128.36 (2 CH_{arom}), 128.47 (CH_{arom}), 128.83 (2 CH_{arom}), 128.88 (2 CH_{arom}), 129.99 (C_{ipso}-SO_2), 130.15 (2 CH_{arom}), 134.15 (C_{ipso}-CH_2), 134.35 (*C*=CH), 146.75 (C_{ipso}-CH_3), 150.06 (N*C*ON), 158.46 (NC=O), 164.64 (CO_2Me).

MS: *m*/*z* (%) = 414 (2) [M$^+$], 383 (4), 259 (32), 155 (94), 121 (3), 104 (5), 91 (100), 77 (8), 65 (29).

Anal. Calcd for $C_{20}H_{18}N_2O_6S$ (414.43): C, 57.96; H, 4.38; N, 6.76. Found: C, 58.00; H, 4.31; N, 6.80.

Methyl (*Z*)-[1-(2-Chlorobenzyl)-2,5-dioxo-3-tosylimidazolidin-4-ylidene]acetate (4b)

White crystals; yield: 0.38 g (85%); mp 127–130 °C.

IR (KBr): 1789 and 1727 (2 C=O, hydantoin), 1657 (CO_2Me), 1585 (C=C), 1555 and 1433 (Ar), 1334 and 1172 (SO_2), 1268 (C–O, ester) cm^{-1}.

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 2.48 (s, 3 H, CH_3), 3.86 (s, 3 H, OMe), 4.77 (s, 2 H, C*H*$_2$Ph), 7.17 (s, 1 H, C=C*H*), 7.11 (d, $^3J_{HH}$ = 7.6 Hz, 1 H_{arom}), 7.17 (t, $^3J_{HH}$ = 7.3 Hz, 1 H_{arom}), 7.22 (t, $^3J_{HH}$ = 7.6 Hz, 1 H_{arom}), 7.33 (d, $^3J_{HH}$ = 7.9 Hz, 1 H_{arom}), 7.39 (d, $^3J_{HH}$ = 8.3 Hz, 2 H_{arom}), 7.95 (d, $^3J_{HH}$ = 8.3 Hz, 2 H_{arom}).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 21.79 (CH_3), 40.77 (*C*H$_2$Ph), 52.85 (OMe), 111.61 (C=*C*H), 127.05 (CH_{arom}), 128.40 (2 CH_{arom}), 129.49 (CH_{arom}), 129.54 (CH_{arom}), 129.82 (CH_{arom}), 129.85 (C_{ipso}-SO_2), 130.17 (2 CH_{arom}), 131.29 (C_{ipso}-Cl), 133.29 (C_{ipso}-CH_2), 134.28 (*C*=CH), 146.82 (C_{ipso}-CH_3), 149.85 (N*C*ON), 158.41 (NC=O), 164.58 (CO_2Me).

MS: *m*/*z* (%) = 448 (1) [M$^+$], 413 (68), 293 (6), 155 (98), 91 (100), 77 (6), 65 (26).

Anal. Calcd for $C_{20}H_{17}ClN_2O_6S$ (448.87): C, 53.52; H, 3.82; N, 6.24. Found: C, 53.70; H, 3.90; N, 6.30.

Methyl (*Z*)-[1-(2-Chlorobenzyl)-2,5-dioxo-3-(phenylsulfonyl)imidazolidin-4-ylidene]acetate (4c)

White crystals; yield: 0.35 g (80%); mp 156–159 °C.

IR (KBr): 1792 and 1732 (2 C=O, hydantoin), 1661 (CO_2Me), 1573 (C=C), 1562 and 1463 (Ar), 1338 and 1170 (SO_2), 1267 (C–O, ester) cm^{-1}.

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 3.86 (s, 3 H, OMe), 4.77 (s, 2 H, C*H*$_2$Ph), 7.06 (s, 1 H, C=C*H*), 7.10 (d, $^3J_{HH}$ = 7.3 Hz, 1 H_{arom}), 7.17 (t, $^3J_{HH}$ = 7.2 Hz, 1 H_{arom}), 7.22 (t, $^3J_{HH}$ = 7.5 Hz, 1 H_{arom}), 7.32 (d, $^3J_{HH}$ = 7.7 Hz, 1 H_{arom}), 7.61 (t, $^3J_{HH}$ = 7.55 Hz, 2 H_{arom}), 7.75 (t, $^3J_{HH}$ = 7.29 Hz, 1 H_{arom}), 8.02 (d, $^3J_{HH}$ = 7.67 Hz, 2 H_{arom}).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 40.84 (*C*H$_2$Ph), 52.87 (OMe), 111.70 (C=*C*H), 127.07 (CH_{arom}), 128.34 (2 CH_{arom}), 129.54 (CH_{arom}), 129.57 (3 CH_{arom}), 129.79 (C_{ipso}-SO_2), 129.83 (CH_{arom}), 131.22 (C_{ipso}-Cl), 133.27 (C_{ipso}-CH_2), 135.31 (CH_{arom}), 137.24 (*C*=CH), 149.77 (N*C*ON), 158.34 (NC=O), 164.50 (CO_2Me).

MS: *m*/*z* (%) = 435 (1) [M$^+$], 399 (92), 293 (7), 141 (58), 91 (7), 77 (100), 65 (11).

Anal. Calcd for $C_{19}H_{15}ClN_2O_6S$ (434.85): C, 52.48; H, 3.48; N, 6.44. Found: C, 52.60; H, 3.55; N, 6.52.

Ethyl (*Z*)-(1-Benzyl-2,5-dioxo-3-tosylimidazolidin-4-ylidene)acetate (4d)

White crystals; yield: 0.37 g (89%); mp 130–131 °C.

IR (KBr): 1790 and 1728 (2 C=O, hydantoin), 1659 (CO_2Me), 1585 (C=C), 1580 and 1482 (Ar), 1326 and 1178 (SO_2), 1255 (C–O, ester) cm^{-1}.

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.35 (t, $^3J_{HH}$ = 7.1 Hz, 3 H, OCH_2CH_3), 2.46 (s, 3 H, CH_3), 4.34 (q, $^3J_{HH}$ = 7.1 Hz, 2 H, OCH_2CH_3), 4.61 (s, 2 H, C*H*$_2$Ph), 7.00 (s, 1 H, C=C*H*), 7.29 (5 H_{arom}), 7.38 (d, $^3J_{HH}$ = 8.0 Hz, 2 H_{arom}), 7.94 (d, $^3J_{HH}$ = 8.0 Hz, 2 H_{arom}).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 13.93 (OCH_2CH_3), 21.78 (CH_3), 43.06 (*C*H$_2$Ph), 62.10 (OCH_2CH_3), 111.86 (C=*C*H), 128.38 (2 CH_{arom}), 128.44 (CH_{arom}), 128.82 (2 CH_{arom}), 128.90 (2 CH_{arom}), 129.75 (C_{ipso}-SO_2), 130.14 (2 CH_{arom}), 134.23 (C_{ipso}-CH_2), 134.38 (*C*=CH), 146.72 (C_{ipso}-CH_3), 150.11 (N*C*ON), 158.45 (NC=O), 164.17 (CO_2Me).

MS: *m*/*z* (%) = 428 (2) [M$^+$], 383 (7), 273 (20), 155 (86), 104 (6), 91 (100), 77 (6), 65 (25).

Anal. Calcd for $C_{21}H_{20}N_2O_6S$ (428.45): C, 58.87; H, 4.70; N, 6.54. Found: C, 58.95; H, 4.82; N, 6.70.

Ethyl (*Z*)-[1-(2-Chlorobenzyl)-2,5-dioxo-3-tosylimidazolidin-4-ylidene]acetate (4e)

White crystals; yield: 0.42 g (90%); mp 144–146 °C.

IR (KBr): 1790 and 1728 (2 C=O, hydantoin), 1660 (CO_2Me), 1585 (C=C), 1555 and 1453 (Ar), 1326 and 1178 (SO_2), 1255 (C–O, ester) cm^{-1}.

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.34 (t, $^3J_{HH}$ = 7.1 Hz, 3 H, OCH_2CH_3), 2.48 (s, 3 H, CH_3), 4.34 (q, $^3J_{HH}$ = 7.1 Hz, 2 H, OCH_2CH_3), 4.77 (s, 2 H, C*H*$_2$Ph), 7.05 (s, 1 H, C=C*H*), 7.10 (d, $^3J_{HH}$ = 7.4 Hz, 1 H_{arom}), 7.17 (t, $^3J_{HH}$ = 7.4 Hz, 1 H_{arom}), 7.22 (t, $^3J_{HH}$ = 7.7 Hz, 1 H_{arom}), 7.33 (d, $^3J_{HH}$ = 7.8 Hz, 1 H_{arom}), 7.39 (d, $^3J_{HH}$ = 7.9 Hz, 2 H_{arom}), 7.95 (d, $^3J_{HH}$ = 8.0 Hz, 2 H_{arom}).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 13.89 (OCH_2CH_3), 21.79 (CH_3), 40.73 (*C*H$_2$Ph), 62.19 (OCH_2CH_3), 112.12 (C=*C*H), 127.03

(CH_{arom}), 128.42 (2 CH_{arom}), 129.46 (CH_{arom}), 129.51 (CH_{arom}), 129.63 (C_{ipso}-SO_2), 129.81 (CH_{arom}), 130.15 (2 CH_{arom}), 131.34 (C_{ipso}-Cl), 133.27 (C_{ipso}-CH_2), 134.34 (*C*=CH), 146.77 (C_{ipso}-CH_3), 149.89 (N*C*ON), 158.39 (NC=O), 164.11 (CO_2Me).

MS: *m*/*z* (%) = 462 (1) [M^+], 427 (68), 417 (7), 307(6), 155 (96), 91 (100), 77 (6), 65 (24).

Anal. Calcd for $C_{21}H_{19}ClN_2O_6S$ (462.90): C, 54.49; H, 4.14; N, 6.05. Found: C, 54.70; H, 4.21; N, 6.10.

Ethyl (*Z*)-[1-Benzyl-2,5-dioxo-3-(phenylsulfonyl)imidazolidin-4-ylidene]acetate (4f)

White crystals; yield: 0.35 g (85%); mp 119–121 °C.

IR (KBr): 1780 and 1736 (2 C=O, hydantoin), 1661 (CO_2Me), 1585 (C=C), 1574 and 1463 (Ar), 1334 and 1167 (SO_2), 1246 (C–O, ester) cm^{-1}.

^1H NMR (500.13 MHz, $CDCl_3$): δ = 1.35 (t, $^3J_{HH}$ = 7.0 Hz, 3 H, OCH_2CH_3), 4.35 (q, $^3J_{HH}$ = 7.0 Hz, 2 H, OCH_2CH_3), 4.61 (s, 2 H, CH_2Ph), 7.02 (s, 1 H, C=C*H*), 7.29 (5 H_{arom}), 7.60 (t, $^3J_{HH}$ = 7.5 Hz, 2 H_{arom}), 7.73 (t, $^3J_{HH}$ = 7.2 Hz, 1 H_{arom}), 8.07 (d, $^3J_{HH}$ = 7.6 Hz, 2 H_{arom}).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 13.91 (OCH_2CH_3), 43.11 (CH_2Ph), 62.13 (OCH_2CH_3), 111.98 (C=*C*H), 128.34 (2 CH_{arom}), 128.48 (CH_{arom}), 128.83 (2 CH_{arom}), 128.87 (2 CH_{arom}), 129.53 (2 CH_{arom}), 129.70 (C_{ipso}-SO_2), 134.17 (C_{ipso}-CH_2), 135.21 (CH_{arom}), 137.38 (*C*=CH), 150.04 (N*C*ON), 158.37 (NC=O), 164.08 (CO_2Me).

MS: *m*/*z* (%) = 414 (3) [M^+], 383 (1), 273 (57), 141 (73), 91 (83), 77 (100), 65 (11).

Anal. Calcd for $C_{20}H_{18}N_2O_6S$ (414.43): C, 57.96; H, 4.38; N, 6.76. Found: C, 58.00; H, 4.52; N, 6.80.

Ethyl (*Z*)-[1-(2-Chlorobenzyl)-2,5-dioxo-3-(phenylsulfonyl)imidazol-4-ylidene]acetate (4g)

White crystals; yield: 0.33 g (80%); mp 144–146 °C.

IR (KBr): 1783 and 1727 (2 C=O, hydantoin), 1716 (CO_2Me), 1655 (C=C), 1556 and 1462 (Ar), 1323 and 1170 (SO_2), 1257 (C–O, ester) cm^{-1}.

^1H NMR (500.13 MHz, $CDCl_3$): δ = 1.34 (t, $^3J_{HH}$ = 7.1 Hz, 3 H, OCH_2CH_3), 4.34 (q, $^3J_{HH}$ = 7.1 Hz, 2 H, OCH_2CH_3), 4.77 (s, 2 H, CH_2Ph), 7.06 (s, 1 H, C=C*H*), 7.10 (d, $^3J_{HH}$ = 7.4 Hz, 1 H_{arom}), 7.17 (t, $^3J_{HH}$ = 7.4 Hz, 1 H_{arom}), 7.22 (t, $^3J_{HH}$ = 7.7 Hz, 1 H_{arom}), 7.33 (d, $^3J_{HH}$ = 7.8 Hz, 1 H_{arom}), 7.61 (t, $^3J_{HH}$ = 7.7 Hz, 2 H_{arom}), 7.75 (t, $^3J_{HH}$ = 7.3 Hz, 1 H_{arom}), 8.08 (d, $^3J_{HH}$ = 7.8 Hz, 2 H_{arom}).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 13.89 (OCH_2CH_3), 40.80 (CH_2Ph), 62.18 (OCH_2CH_3), 112.21 (C=*C*H), 127.06 (CH_{arom}), 128.37 (2 CH_{arom}), 129.51 (CH_{arom}), 129.56 (3 CH_{arom}), 129.70 (C_{ipso}-SO_2), 129.82 (CH_{arom}), 131.27 (C_{ipso}-Cl), 133.27 (C_{ipso}-CH_2), 135.28 (CH_{arom}), 137.29 (*C*=CH), 149.82 (N*C*ON), 158.32 (NC=O), 164.04 (CO_2Me).

MS: *m*/*z* (%) = 447 (3) [M^+], 413 (83), 417 (7), 407(4), 227(32), 141 (53), 77 (100), 65 (6).

Anal. Calcd for $C_{20}H_{17}ClN_2O_6S$ (448.87): C, 53.52; H, 3.82; N, 6.24. Found: C, 53.60; H, 3.91; N, 6.35.

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