The First aza-Wittig Reaction Involving a non-Cumulated Sulfoxy Group

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Abstract: 3-(Aryliminophosphoranyl)-5-phenyl-4-arylsulfoxy-isoxazoles undergo ring closure via an intramolecular aza-Wittig type reaction of an iminophosphorane onto a non-cumulated sulfoxide. The products obtained are isoxazolo[4,3-*c*]-2,1-benzothiazines, a hitherto unreported heterocyclic system. This is the first example of the construction of the sulfimide linkage (S=N) via a Wittig type process involving non-cumulated sulfoxides. The requisite iminophosphoranes were synthesised using the Staudinger reaction of an azide with triphenylphosphine. Other key steps include the regioselective addition of a carbanion to a nitrile oxide in the presence of an azide, and the synthesis and use of the little reported *o*-azidobenzonitrile oxide.

Key words: aza-Wittig reaction, sulfoxides, 1,3-dipolar cycloadditions, sulfimide, 2,1-benzothiazine

The aza-Wittig reaction[1] is the nitrogen analogue of the Wittig olefination process and involves the reaction of an iminophosphorane[2] with a carbonyl. The reaction is of use in the synthesis of acyclic imines,[3] and in the intramolecular formation of carbon-nitrogen double bonds in heterocyclic synthesis.[4] The use of iminophosphoranes in other aza-Wittig type reactions for the formation of heterobonds other than C=N is rare. In particular, the only examples that detail the synthesis of the N=S (sulfimide) bond involve the use of cumulated S=O functionality.[5] The synthesis of sulfimides (also known as sulfilimines or iminosulfuranes)[6] is the focus of much interest,[6–8] particularly in the development of new reagents for asymmetric catalysis. Whilst sulfoxides are often used for the synthesis of acyclic sulfimides,[7] the corresponding intramolecular sulfoxide reactions, leading to cyclic sulfimides, have not been reported to the best of our knowledge, although several methods for the cyclisation of sulfoxides into the well known cyclic sulfoximides [–S(=O)(=NR)–] are known.[9] Intermolecular[8] and intramolecular[10] methods for the sulfimidation of sulfides, the later leading to cyclic sulfimides have been reported. Other methods for the synthesis of cyclic sulfimides involve the use of sulfuryl halides,[11] thiazyl fluoride[12] and trithiazyl trichloride.[13] Sulfimides are also of interest because of their inherent biological activity,[14] and as precursors, via oxidation, to the synthetically[15] and biologically[9,15] useful sulfoximides. In a continuation of our studies[3b,4c] in the area of aza-Wittig chemistry, in this letter we report the first example of the synthesis of a cyclic sulfimide involving an intramolecular aza-Wittig type ring-closure process between a sulfoxide and an iminophosphorane. This is the first example of an aza-Wittig type reaction between an iminophosphorane and a non-cumulated 'S=O' bond.

Our interest in this area was aroused by our investigations into the chemistry of 2-[(*o*-iminophosphoranyl)benzenesulfonyl]-1,2-thiazine-1-oxides **1** (R^1, R^2, R^3, R^4 = H or Me or Ph), species that we have previously converted into benzothiadiazepines using chemistry developed in this laboratory that has been reported elsewhere.[4c] In the current study, 2-[(*o*-iminophosphoranyl)benzenesulfonyl]-1,2-thiazine-1-oxides **1**, Scheme 1, were heated in toluene the strict absence of water, and it was noted (NMR tube experiment) that triphenylphosphine oxide was formed. We assign this to the putative aza-Wittig type reaction shown in Route A of Scheme 1. We were unable to isolate the proposed initial heterocyclic product **2** of this reaction, but could isolate, after silica gel chromatography, *o*-aminobenzenesulfonamide, triphenylphosphine oxide and, occasionally (see below), dienes. The formation of *o*-aminobenzenesulfonamide is intriguing, and we believe it may arise as a result of intermediate **2** undergoing a retro-Diels–Alder reaction followed by ready hydrolysis, on the column, of the resultant cyclic sulfur diimide species **3**.

With 1,2-thiazine-1-oxides **1** (R^1 = R^4 = Ph; R^2 = R^3 = H) and **1a** (see Scheme 3), we could isolate dienes from the reaction mixture in yields of 76% and 70%, respectively, as shown for 1,2-thiazine-1-oxide **1a** in Scheme 2.

We cannot, of course, exclude the possibility that species **1** undergo retro-Diels–Alder reaction first to give the iminophosphoranyl heterocumulene **4**, and then aza-Wittig type reaction to furnish the cyclic sulfur diimide **3**, as shown in Route B of Scheme 1. However, a sample of iminophosphoranyl heterocumulene **4**, synthesised either from the Staudinger reaction of the corresponding azide or from sulfinylation[16] of the corresponding iminophosphoranyl sulfonamide, when subjected to the identical reaction conditions did not give *o*-aminobenzenesulfonamide, thus indicating that Route A is followed. Despite the instability of the heterocyclic aza-Wittig adducts **2**, these observations gave us our first hint that an iminophosphorane could react in an intramolecular fashion with a non-cumulated S=O functionality, and prompted further investigation.

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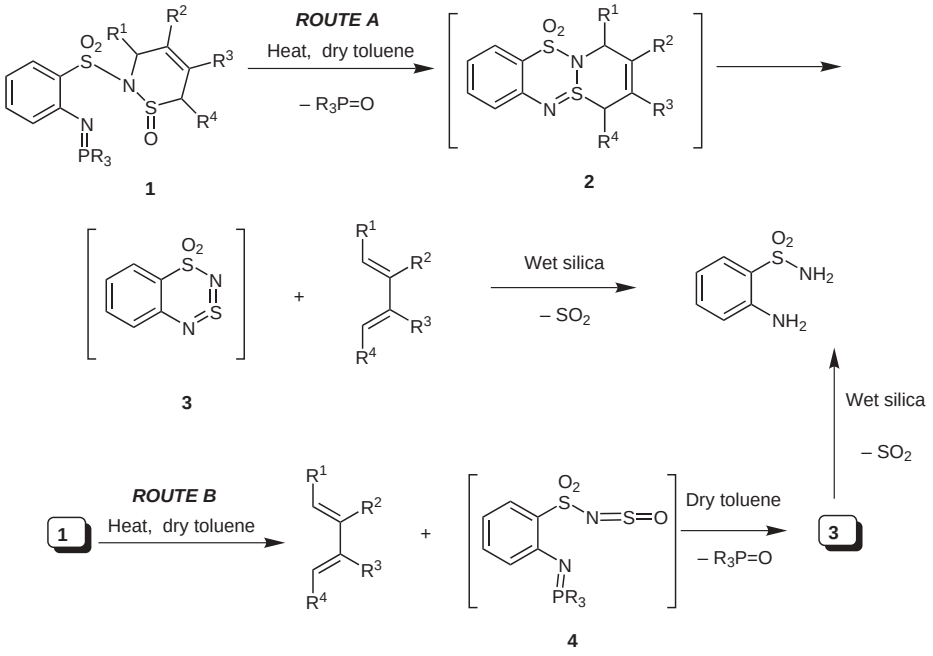
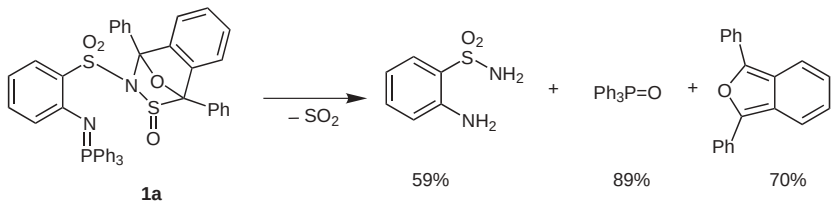
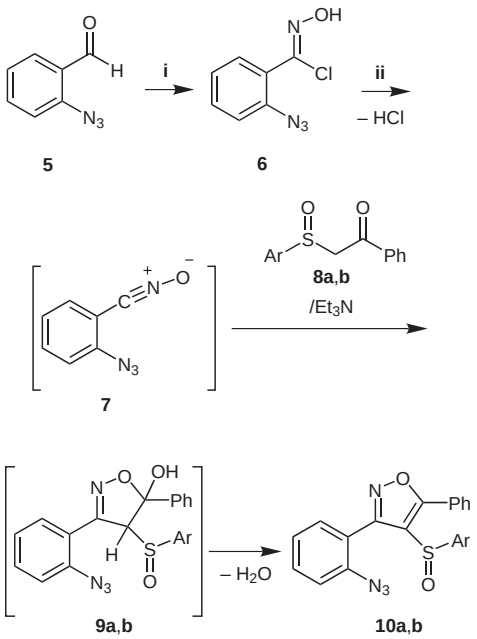


Scheme 1 Formation of *o*-aminobenzenesulfonamide from 1,2-thiazine-1-oxides **1**.



Scheme 2 The products of thermolysis of 1,2-thiazine-1-oxide **1a**.

We hence focused our attention on bringing about an intramolecular reaction between an iminophosphorane and a sulfoxide that would give a stable heterocyclic product. Iminophosphoranes are most easily accessed by the Staudinger reaction between an azide and a phosphine or phosphite.[2] Thus, our initial target was to synthesise an azide bearing a tethered sulfoxide group. We decided to use the readily available *o*-azidobenzaldehyde[17] as the starting material, with a view to installing the sulfoxide tether via elaboration of the aldehyde functionality. Attempted olefination of the aldehyde via the Wittig reaction and attempted aldol condensations were unsuccessful, possibly due to the interaction of the azide with the carbanions, a known reaction of the azide group.[18] We therefore chose to convert the aldehyde into a chloro oxime and thence into a nitrile oxide, as it had previously been shown that *o*-azidobenzonitrile oxide reacts with carbanions solely via its nitrile oxide function.[19] The conversion of *o*-azidobenzaldehyde (**5**) into chloro oxime **6** via the oxime proceeded in high yield (two steps: 92% and 95%) without incident, as shown in Scheme 3.

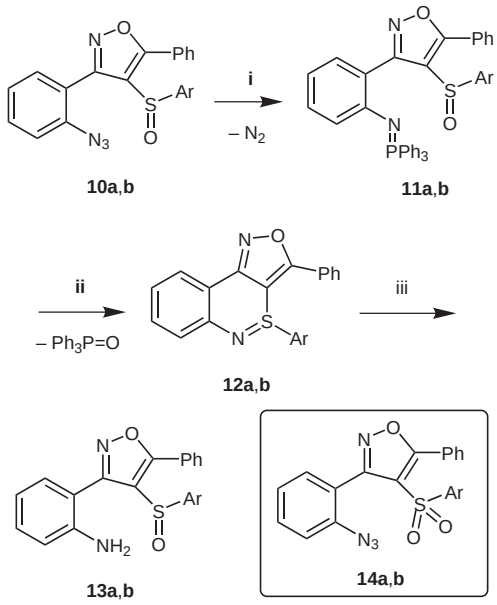


Scheme 3 *Reagents and conditions*: (i) $NH_2OH{\cdot}HCl$, NaOAc, EtOH, 25 °C then NCS, $CHCl_3$, C_5H_5N, 25 °C; (ii) Et_3N, EtOH, 25 °C.

The reaction of the chloro oxime **6** with the β-keto sulfoxides **8a** (Ar = *p*-Tol) and **8b** (Ar = Ph) in the presence of triethylamine gave the 3-azidoaryl-4-sulfoxy-isoxazoles

10a (Ar = *p*-Tol) and **10b** (Ar = Ph) in 46% and 52% yields, respectively. The only other products recovered were small amounts of the nitrile oxide dimer and unreacted β-keto sulfoxide, thereby demonstrating that carbanions/enolates derived from β-keto sulfoxides do indeed react regiospecifically with *o*-azidobenzonitrile oxide. This reaction proceeds via the generation of a carbanion/enolate and its addition to the nitrile oxide **7**, both species being generated in-situ. Subsequent loss of water from the adducts **9** gives the isoxazoles **10**.[20]

The Staudinger reaction between the 3-(*o*-azidophenyl)-4-sulfoxyaryl-isoxazoles **10** and triphenylphosphine, shown in Scheme 4, gave the corresponding aryliminophosphoranyl 4-sulfoxyaryl-isoxazoles[21] **11a** (Ar = *p*-Tol) and **11b** (Ar = Ph) in yields of 91% and 95%. Treatment of compounds **11** in anhydrous toluene at reflux for 5–8 hours gave, after column chromatography, an 80–85% yield of triphenylphosphine oxide together with the isoxazolo[4,3-*c*][2,1]benzothiazines **12a** (Ar = *p*-Tol) and **12b** (Ar = Ph), a hitherto unreported heterocyclic system, in yields of 50% and 48%, respectively.[22]



Scheme 4 *Reagents and conditions*: (i) PPh_3, THF, 25 °C; (ii) reflux, toluene, 5 h; (iii) THF, H_2O (10%), 25 °C, 16 h.

The isoxazolo[4,3-*c*]-2,1-benzothiazines **12a** and **12b** were sufficiently stable to allow characterisation by mass spectrometry (including HRMS), infra-red spectroscopy, micro-analysis and ^1H NMR and ^{13}C NMR spectroscopy.[22] Treatment of isoxazolo[4,3-*c*][2,1]benzothiazines **12** in wet THF at room temperature gave the hydrolysis products **13**, in high yield,[23] further confirming our structural assignment.

Attempted Staudinger reaction and subsequent aza-Wittig type ring closure of 3-(*o*-azidoaryl)-4-arylsulfonyl-isoxazoles **14** was unsuccessful, showing that the corresponding sulfone will not undergo the analogous reaction. The requisite sulfones **14** were easily synthesised from the reaction of chloro oxime **6** with the relevant β-keto sulfone. Previous work by one of us has shown that iminophosphoranyl sulfones derived from saccharin similarly show no evidence of cyclisation at the sulfone group.[24]

To summarise, the cyclisation of 3-(aryliminophosphoranyl)-4-sulfoxyaryl-isoxazoles via an intramolecular aza-Wittig type reaction resulted in the formation of cyclic sulfimides, giving the hitherto unreported heterocyclic system, the isoxazolo[4,3-*c*]-2,1-benzothiazine. This is the first example of a non-cumulated sulfoxy system undergoing an aza-Wittig type reaction. Work on the use of optically pure sulfoxides in the reaction is underway and further applications to the synthesis of other heterocyclic systems as well as intermolecular versions of the reaction are being explored.

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(20) **Synthesis of 3-(*o*-Azidophenyl)-4-(*p*-tolylsulfoxy)-5-phenylisoxazole (10a):** To a solution of phenacyl *p*-tolyl sulfoxide (1.3140 g, 5.09 mmol, 1 equiv) and freshly distilled Et_3N (1.42 mL, d = 0.726, 10.17 mmol, 2 equiv) in anhyd EtOH (15 mL) was added, dropwise over 4 h, a solution of *o*-azido benzohydroximoyl chloride (1.0000 g, 5.09 mmol, 1 equiv) in anhyd EtOH (15 mL), under an atmosphere of dry nitrogen. The mixture was concentrated in vacuo and the crude residue was purified by flash silica column chromatography (eluent: petroleum ether–EtOAc, 3:1) to give 3-(*o*-azidophenyl)-4-(*p*-tolylsulfoxy)-5-phenylisoxazole as a yellow solid (0.9470 g, 46% yield), mp 148–149 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.17 (s, 3 H, Me), 7.04 (t, 1 H, *J* = 7.5 Hz, 1 × ArH), 7.07 (d, 2 H, *J* = 8.2 Hz, 2 × ArH), 7.12 (d, 2 H, *J* = 8.2 Hz, 2 × ArH), 7.19 (dt, 1 H, *J* = 7.5, 0.7 Hz, 1 × ArH), 7.45 (m, 2 H, 2 × ArH), 7.57 (m, 3 H, 3 × ArH), 8.08, (dd, 2 H, *J* = 8.1, 1.7 Hz, 2 × ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1 (CH_3), 118.0 (CH), 118.7 (quat.), 119.1 (quat.), 124.3 (CH), 124.4 (CH), 125.6 (quat.), 128.8 (quat.), 128.9 (CH), 129.0 (CH), 131.3 (CH), 131.9 (CH), 132.6 (CH), 137.7 (quat.), 138.8 (quat.), 140.5 (quat.), 160.1 (quat.), 172.5 (quat.). IR: 2925 (m), 2128 (s), 1604 (w), 1581 (w), 1556 (m), 1448 (m), 1300 (s), 1084 (m), 1054 (m) cm^{-1}. MS (EI): *m/z* (%) = 372 (100) [M – 28], 237 (80), 189 (70), 119 (30), 91 (40), 77 (98). HRMS (ES+): found MH^+ 401.1066, $C_{22}H_{16}N_4O_2S$ requires MH 401.1072.

(21) **Synthesis 3-[*o*-*N*-(Triphenylphosphoranylidene)phenyl]-4-(*p*-tolylsulfoxy)-5-phenylisoxazole (11a):** To a solution of 3-(*o*-azidophenyl)-4-(*p*-tolyl-sulfoxy)-5-phenyl-isoxazole (**10a**) (0.2000 g, 0.50 mmol, 1 equiv) in anhyd toluene (10 mL) was added at r.t., under an atmosphere of dry nitrogen, a solution of triphenylphosphine (0.1311 g, 0.50 mmol, 1 equiv) in anhyd toluene (5 mL). The reaction mixture was stirred for a total of 5 h whilst being monitored by TLC. After completion of the reaction, the solvent was removed in vacuo and the crude product was purified by flash silica column chromatography (eluent: petroleum ether–EtOAc, 2:1) to give 3-[*o*-*N*-(triphenylphosphoranyl-idene)phenyl]-4-(*p*-tolylsulfoxy)-5-phenylisoxazole as a bright yellow solid (0.2890 g, 91% yield), mp 102–104 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.16 (s, 3 H, Me), 6.54 (d, 1 H, *J* = 8.25 Hz, 1 × ArH), 6.74 (t, 1 H, *J* = 7.5 Hz, 1 × ArH), 6.81 (d, 2 H, *J* = 8.1 Hz, 2 × ArH), 7.03 (td, 1 H, *J* = 7.7, 1.7 Hz, 1 × ArH), 7.14 (d, 2 H, *J* = 8.1 Hz, 2 × ArH), 7.27–7.46 (m, 10 H, 10 × PhH), 7.50 (m, 3 H, 3 × ArH), 7.73–7.85 (m, 6 H, 6 × ArH), 8.13 (dd, 2 H, *J* = 7.7, 1.9 Hz, 2 × ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1 (CH_3), 116.7 (CH), 121.1 (CH), 121.3 (CH), 124.4 (CH), 126.8 (quat.), 126.9 (quat.), 128.3 (CH), 128.4 (CH), 128.5 (CH), 129.3 (CH), 130.0 (quat.), 130.3 (CH), 130.4 (CH), 130.5 (CH), 130.9 (CH), 131.0 (CH), 131.6 (CH), 132.0 (quat.), 132.1 (quat.), 132.7 (CH), 132.8 (CH), 139.7 (quat.), 140.4 (quat.), 150.7 (quat.), 164.8 (quat.), 171.1 (quat.). IR: 3018 (m), 1677 (m), 1606 (m), 1560 (m), 1438 (m), 1345 (m), 1181 (s), 1119 (m), 694 (m), 666 (m) cm^{-1}. HRMS (ES+): found MH^+ 635.1928, $C_{40}H_{31}N_2O_2PS$ requires MH^+ 635.1922.

(22) **Synthesis of 3-Phenyl-2-(*p*-tolyl)-isoxazolo[4,3-*c*][2,1]benzothiazine (12a):** A solution of 3-[*o*-*N*-(triphenylphosphoranylidene)phenyl]-4-(*p*-tolylsulfoxy)-5-phenylisoxazole (**11a**) (0.2500 g, 0.3939 mmol, 1 equiv) in freshly distilled anhyd toluene (10 mL) was heated at reflux under a dry nitrogen atmosphere for a total of 8 h, whilst being monitored by TLC. After completion of the reaction, the solvent was removed in vacuo and the crude product was purified by flash silica column chromatography (eluent: petroleum ether–EtOAc, 5:1) to give 3-phenyl-2-(*p*-tolyl)-isoxazolo[4,3-*c*][2,1]benzothiazine as a bright green oil (0.0700 g, 50% yield), a sample of which solidified on standing. CHN: found (%) C, 74.4; H, 4.4; N, 7.6; S, 9.5. $C_{22}H_{16}N_2OS$ requires (%): C, 74.1; H, 4.5; N, 7.9; S, 9.0. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.17 (s, 3 H, Me), 6.53 (d, 2 H, *J* = 8.1 Hz, 2 × ArH), 6.71, (d, 2 H, *J* = 8.1 Hz, 2 × ArH), 7.11 (t, 1 H, *J* = 7.5 Hz, 1 × ArH), 7.33 (t, 1 H, *J* = 7.4 Hz, 1 × ArH), 7.40 (m, 3 H, 3 × ArH), 7.52 (t, 1 H, *J* = 7.3 Hz, 1 × ArH), 7.83 (d, 1 H, *J* = 7.9 Hz, 1 × ArH), 8.20 (d, 2 H, *J* = 7.4 Hz, 2 × ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0 (CH_3), 110.8 (CH), 121.0 (CH), 122.3 (CH), 123.7 (quat.), 127.5 (CH), 128.5 (CH), 128.9 (CH), 129.3 (CH), 129.6 (CH), 133.1 (CH), 133.3 (quat.), 135.9 (quat.), 137.6 (quat.), 144.7 (quat.), 145.7 (quat.), 168.2 (quat.). IR: 3019 (m), 2925 (m), 1681 (m), 1596 (m), 1478 (m) 1449 (m), 908 (s),

805 (m), 668 (m) cm^{-1}. MS (ES+): *m/z* (%) = 379 (100) [M + 23]. HRMS (ES+): found MH^+ 357.1058, $C_{22}H_{16}N_2OS$ requires MH^+ 357.1056.

(23) **Synthesis of 3-(*o*-aminophenyl)-5-(phenyl)-4-(*p*-tolylsulfoxy)-isoxazole (13a):** To a solution of the 3-phenyl-2-(*p*-tolyl)-isoxazolo[4,3-*c*][2,1]benzothiazine (**12a**) (0.0500 g, 0.14 mmol) in THF (5 mL) was added, at r.t., H_2O (1 mL). The reaction mixture was stirred for a total of 20 h whilst being monitored by TLC. After completion of the reaction, the solvent was removed in vacuo and the crude product was purified by flash column chromatography (eluent: petroleum ether–EtOAc, 5:3) to give 3-(*o*-aminophenyl)-5-(phenyl)-4-(*p*-tolylsulfoxy)-isoxazole as a pale yellow oil (0.0452 g, 86% yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.27 (s, 3 H, Me), 4.43 (broad s, 2 H, NH_2), 6.59 (d, 1 H, *J* = 8.0 Hz, 1 × ArH), 6.65 (t, 1 H, *J* = 7.5 Hz, 1 × ArH), 7.10 (t, 1 H, *J* = 7.3 Hz, 1 × ArH), 7.20 (m, 3 H, 3 × ArH), 7.26 (m, 3 H, 3 × ArH), 7.36 (d, 2 H, *J* = 8.1 Hz, 2 × ArH), 7.94 (d, 2 H, *J* = 8.2 Hz, 2 × ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6 (CH_3), 111.8 (quat.), 116.0 (CH), 117.5 (quat.), 117.6 (CH), 122.8 (quat.), 124.3 (CH), 128.3 (CH), 128.8 (CH), 129.7 (CH), 130.0 (CH), 130.8 (CH), 132.0 (CH), 140.6 (quat.), 142.6 (quat.), 145.3 (quat.), 161.5 (quat.), 173.8 (quat.). IR: 3476 (m, broad), 3381 (m, broad), 3062 (m), 2925 (w), 1671 (s), 1580 (m), 1557 (m), 1499 (s), 1475 (m), 1444 (m), 1374 (m), 1083 (m), 1038 (s), 668 (m)cm^{-1}. MS (ES+): *m/z* (%) = 375 (100) [M + H], 397 (55) [M + Na]. HRMS (ES+): found MH^+ 375.1172, $C_{22}H_{18}N_2O_2S$ requires MH 375.1167.

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