Unexpected new examples of the Thyagarajan-Majumdar tandem cyclization of aryl propargyl sulfoxides

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Dedicated to Prof. Rosa M. Claramunt on the occasion of her 65th anniversary

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Abstract

We observed an unexpected cyclization of aryl propargyl sulfoxides to 1-benzothiophenes while attempting the in situ preparation of a particular class of allenyl sulfoxides as substrates for intramolecular hydride-shift experiments. A mechanistic rationale for explaining this result, involving a sequence of [2,3] and [3,3] sigmatropic rearrangements and a final conjugate addition, is provided by the previous work of Thyagarajan and Majumdar.

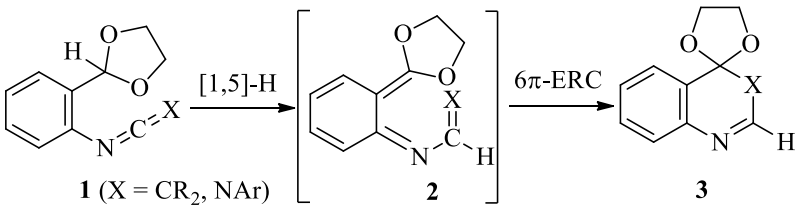
Keywords: cyclization, sigmatropic rearrangement, propargyl sulfoxide, 1-benzothiophene

Introduction

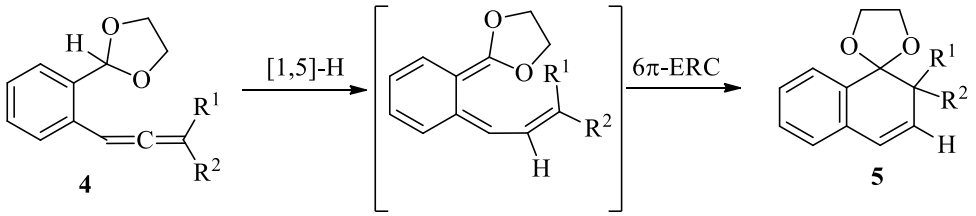
During the last few years our research group has become involved in the investigation of the hydride donor ability of acetalic functions in a series of intramolecular processes. In these reactions the released hydride is transferred to the electrophilic central carbon atom of certain heterocumulene fragments (ketenimines, carbodiimides) and other electrophilic functions. Gratifyingly, we have shown that several of such hydride-like [1,4] and [1,5]-H shifts occur under mild reaction conditions, this migration step being habitually followed by a subsequent pericyclic transformation, most usually a 6π electrocyclic ring-closure (6π-ERC).[1-5] Thus, for example, the [1,5]-H shift step in acetal-ketenimines (X = CR_2) and acetal-carbodiimides (X = NAr) **1** leads to the *o*-azaxylylene intermediates **2**, which quickly undergo a 6π-electro-cyclization to give quinolines and quinazolines **3** respectively (Scheme 1).

Following our efforts in this area, we reasoned that related tandem processes are conceivable by replacing the heterocumulenic hydride-acceptor unit by other electrophilic functional groups, while keeping the acetal function as the hydride-releasing fragment. In this line, we assumed that the *sp*-hybridized central carbon atom of an allene moiety might also act as the terminus of a

similar 1,5-hydride shift from an acetal function, thus promoting sequential transformation from acetal-allenes **4** to spirodioxolanes **5** (Scheme 2), closely related with those shown in Scheme 1.



Scheme 1. Previously studied tandem processes in acetal-ketenimines and acetal-carbodiimides.



Scheme 2. Proposed [1,5]-H/ 6π-ERC tandem sequence in acetal-allenes

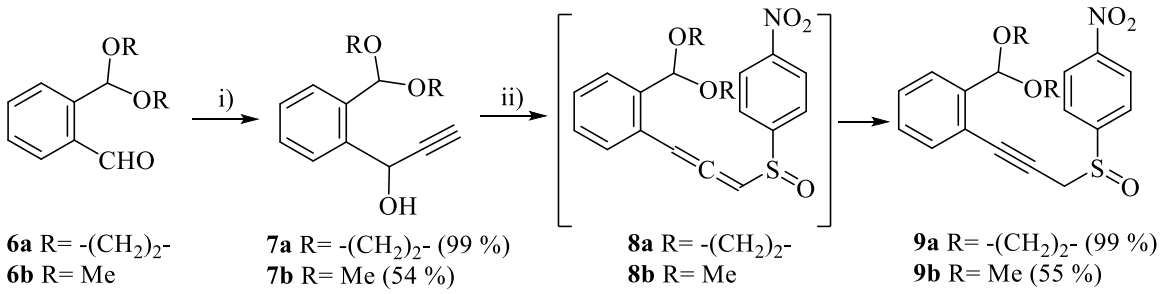
In order to secure the electrophilic character of the central carbon atom of the cumulenic function in **4** we decided to synthesize acetal-allenes bearing electron-withdrawing functions, such as the sulfoxide group, at the terminal carbon atom of the allene fragment.

Surprisingly, when we attempted the *in situ* preparation of a particular class of sulfoxide-substituted acetal-allenes from the respective propargylic sulfoxides, built on an *ortho*-phenylene scaffold bearing an hydride-releasing acetal function, an unexpected cyclization of the aryl propargyl sulfoxide moiety took place instead of the presumed [1,5]-H/6π-ERC tandem process.

Results and Discussion

The reaction of 2-(1,3-dioxolan-2-yl)benzaldehyde **6a** and its dimethoxy analogues **6b** with ethynylmagnesium bromide in anhydrous tetrahydrofuran at 0 ºC for 40 minutes, afforded the corresponding propargylic alcohols **7** in moderate to excellent yields (54-99%). By treatment with *para*-nitrobenzenesulfenyl chloride in the presence of triethylamine in anhydrous tetrahydrofuran at -78 ºC for 1 h, alcohols **7** were converted into the respective sulfenate esters, which experienced the well-known [2,3] sigmatropic rearrangement to the allenyl sulfoxides **8**.[6,7] Under the reaction conditions, the desired but elusive allenes **8** isomerized to the more stable propargyl sulfoxides **9** in good yields (55-99 %) (Scheme 3).

With the aim of promoting the designed hydride shift in a putative equilibrium fraction of acetal-allenes **8** we heated toluene solutions of the propargylic sulfoxides **9** in the presence of a catalytic amount of Et_3N (10 %) for 5 h. To our surprise, the reaction products were mixtures of the 3-aroyl-2,3-dihydro-1-benzothiophenes **10** and 3-aroyl-1-benzothiophenes **11**, which differ only in the degree of hydrogenation at the five-membered ring. In these mixtures the dihydro derivatives **10** were always the major components, obtained in 41-43 % yield (Scheme 4).



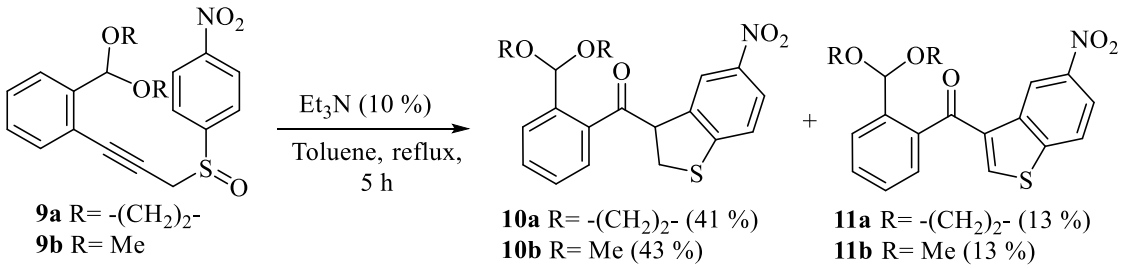
6a R= -$(CH_2)_2$-
6b R= Me

7a R= -$(CH_2)_2$- (99 %)
7b R= Me (54 %)

8a R= -$(CH_2)_2$-
8b R= Me

9a R= -$(CH_2)_2$- (99 %)
9b R= Me (55 %)

Scheme 3. *Reagents and conditions:* i) HC≡CMgBr, THF, 0 ºC, 40 min; ii) 4-NO_2-C_6H_4-SCl, Et_3N, THF, -78 ºC → rt, 3 h



9a R= -$(CH_2)_2$-
9b R= Me

10a R= -$(CH_2)_2$- (41 %)
10b R= Me (43 %)

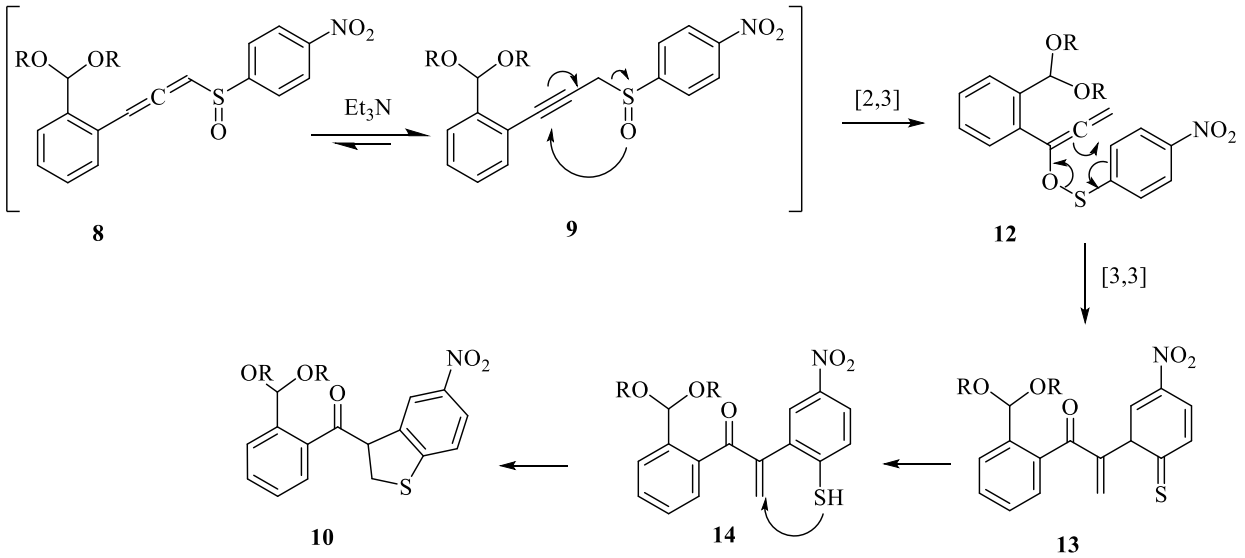
11a R= -$(CH_2)_2$- (13 %)
11b R= Me (13 %)

Scheme 4. Synthesis of 2,3-dihydro-1-benzothiophenes **10** and 1-benzothiophenes **11**

The formation of the 3-acyl-1-benzothiophene unit present in **10** and **11** only involves the aryl propargyl sulfoxide moiety, and may be rationalized by a mechanism involving as a first step a [2,3]-sigmatropic rearrangement of the propargyl sulfoxide function to give the allenyl-sulfenate **12** followed by a [3,3]-sigmatropic rearrangement and further tautomerization of the initially formed thione **13** leading to the thiol-enone intermediate **14**. Finally, an internal conjugate nucleophilic addition of the thiol group to the C =C bond of the enone fragment in **14** would account for the formation of the 3-aroyl-2,3-dihydro-1-benzothiophenes **10**. Clearly, a proportion of **10** seems to become air-oxidized to the fully aromatic 1-benzothiophenes **11** (Scheme 5).

From the results of these experiments, it seems that this type of tandem cyclization in **9** is globally faster than the desired hydride migration in acetal-allene **8**, thus precluding the occurrence of this latter transformation, as far as an equilibrium fraction of **8** is present in the toluene solution of **9**.

Following the experimental study showing the conversion of sulfoxides **9** into benzothiophenes **10** and **11** we carried out an extensive bibliographic search, finding out a similar transformation previously reported by Thyagarajan and Majumdar, who explained this type of tandem cyclization by the mechanism represented in Scheme 5. A recent review on this transformation is available,[8] disclosing that it was first reported in 1972 as result of the PhD work of K. C. Majumdar under the supervision of Professor B. S. Thyagarajan.[9,10] As summarized in that review, this synthetic strategy has been scarcely utilized, almost exclusively by the research groups of its two discoverers. This is why, as indicated in the title of this article, we propose this type of one-pot conversion of aryl propargyl sulfoxides into benzo[*b*]thien-3-yl ketones to be named as the Thyagarajan-Majumdar tandem cyclization.



Scheme 5. Mechanism of the conversion **9** → **10.**

Conclusions

In this communication we have summarized our results on what we interpret as an unexpected cyclization involving an aryl propargyl sulfoxide fragment, which was in fact a reaction already in the literature, although not widely known. We have proposed this reaction to be named after its discoverers.

Experimental Section

General Methods. All melting points are uncorrected. Infrared (IR) spectra were recorded as Nujol emulsions or neats.^{1}H NMR spectra were recorded in $CDCl_3$ or CD_2Cl_2 at 300 or 400

MHz. ^{13}C NMR spectra were recorded in $CDCl_3$ or CD_2Cl_2 at 75 or 100 MHz. The chemical shifts are expressed in ppm, relative to Me_4Si at δ = 0.00 ppm for ^1H, while the chemical shifts for ^{13}C are reported relative to the resonance of $CDCl_3$ δ = 77.1 ppm or CD_2Cl_2 δ = 54.0 ppm. Mass spectra were recorded on a HPLC/MS TOF 6220 Agilent Technologies apparatus.

Materials: 2-(1,3-Dioxolan-2-yl)benzaldehyde (**6a**)[11] and 2-(dimethoxymethyl)benzaldehyde (**6b**)[12] were prepared according to previously reported procedures.

Preparation of propargylic alcohols 7

To a solution of the 2-(1,3-dioxolan-2-yl)benzaldehyde **6a** (0.53 g, 3 mmol) or 2-(dimethoxy methyl)benzaldehyde **6b** (0.54 g, 3 mmol) in anhydrous tetrahydrofuran (30 mL), under nitrogen and at 0 ºC, 0.5 M solution of ethynylmagnesium bromide in THF (6 mL, 3 mmol) was added. The reaction mixture was stirred at 0 °C for 40 min. Then a saturated aqueous solution of NH_4Cl (10 mL) was added and the resulting mixture was extracted with dichloromethane (2 × 30 mL). The combined organic layers were washed with water (2 × 100 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the resulting oil was purified by silica gel column chromatography.

1-[2-(1,3-Dioxolan-2-yl)phenyl]prop-2-yn-1-ol (**7a**). eluent for column chromatography: hexane/diethyl ether (1:1 v/v); yield 99%; 0.66 g; yellow oil; IR (Neat): ν = 3417 (vs), 3288 (vs), 1456 (s), 1405 (s), 1220 (s), 1112 (s), 1076 (s), 1022 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.65 (1H, d, *J* = 2.5 Hz), 3.79 (1H, br s), 3.98-4.07 (2H, m), 4.08-4.17 (2H, m), 5.81 (1H, s), 6.14 (1H, br s), 7.32-7.44 (2H, m), 7.56 (1H, dd, *J* = 1.8, 7.3, Hz), 7.78 (1H, dd, *J* = 1.8, 7.3 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 61.7, 65.0, 65.1, 74.8, 82.8 (s), 102.3, 127.2, 128.4, 128.5, 129.7, 134.2 (s), 138.7 (s), ppm; HRMS (ESI): *m/z* calcd for $C_{12}H_{12}NaO_3$ $[M+Na]^+$ 227.0679; found: 227.0679.

1-[2-(Dimethoxymethyl)phenyl]prop-2-yn-1-ol (**7b**). eluent for column chromatography: hexane/diethyl ether (1:1, v/v); yield: 54%; 0.33 g; pale yellow oil; IR (Neat) ν = 3403 (vs), 2937 (vs), 1454 (vs), 1401 (s), 1382 (vs), 1354 (vs), 1284 (s), 1192 (vs) cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ = 2.70 (1H, m), 3.38 (3H, s), 3.39 (3H, s), 3.68 (1H, s), 5.66 (1H, s), 5.89 (1H, s), 7.38-7.44 (2H, m), 7.53-7.55 (1H, m), 7.77-7.79 (1H, m) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2) δ = 54.3, 54.4, 62.2, 74.8, 84.1 (s), 103.9, 128.3, 128.7, 128.8, 129.7, 135.8 (s), 139.1 (s) ppm; HRMS (ESI): *m/z* calcd. for $C_{12}H_{14}NaO_3$ $[M + Na]^+$ 229.0835; found 229.0830.

Synthesis of propargylic sulphoxides 9

To a solution of the appropriate propargylic alcohol **7** (3.5 mmol) and triethylamine (1 mL, 7 mmol) in anhydrous THF (10 mL) cooled at -78 °C 4-nitrobenzenesulfenyl chloride (0.55 g, 3.8 mmol) was added. The reaction mixture was stirred at -78 °C for 1 h. Then, the reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (20 mL), and extracted with dichloromethane (2 × 30 mL). The organic layers were combined, washed with water (50 mL), and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography.

2-[2-[3-(4-Nitrophenylsulfinyl)prop-1-ynyl]phenyl]-1,3-dioxolane (**9a**). Eluent for column chromatography: ethyl acetate; yield 99%; 1.2 g; colorless prisms; m.p: 103-105 ºC (diethyl ether); IR (Nujol): ν = 1603 (s), 1525 (vs), 1344 (vs), 1317 (m), 1198 (vs) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.93-4.05 (4H, m), 4.08-4.18 (2H, m), 5.93 (1H, s), 7.31-7.34 (2H, m), 7.37-7.43 (1H, m), 7.57 (1H, d, *J* = 7.8 Hz), 7.96-8.01 (2H, m), 8.36-8.40 (2H, m) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 49.1, 65.6, 81.4 (s), 86.5 (s), 101.6, 120.8 (s), 124.1, 125.9, 126.3, 129.2, 129.5, 132.9, 139.6 (s), 150.0 (s), 150.5 (s) ppm; HRMS (ESI): *m/z* calcd for $C_{18}H_{16}NO_5S$ $[M+H]^+$ 358.0744; found: 358.075.

1-(Dimethoxymethyl)-2-[3-(4-nitrophenylsulfinyl)prop-1-ynyl]benzene (**9b**). Eluent for column chromatography: hexane/ethyl acetate (1:4 v/v); yield 55%; 0.68 g; colorless prisms; m.p: 105-107 ºC (diethyl ether); IR (Nujol): ν = 1600 (s), 1519 (vs), 1400 (s), 1339 (vs), 1202 (vs), 1112 (vs), 1093 (vs), 1034 (vs) cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2): δ = 3.27 (6H, s), 4.01 (2H, s), 5.50 (1H, s), 7.24-7.37 (3H, m), 7.54 (1H, dd, *J* = 0.8, 8.0 Hz), 7.94-7.97 (2H, m), 8.32-8.36 (2H, m) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 49.4, 53.7, 53.8, 82.3 (s), 86.7 (s), 102.0, 121.0, 124.5, 126.3, 127.0, 128.9, 129.2, 133.2, 140.5 (s), 150.4 (s), 151.4 (s) ppm; HRMS (ESI): *m/z* calcd for $C_{18}H_{17}NNaO_5S$ $[M+Na]^+$ 382.0720; found: 382.0726.

Synthesis of 1-benzothiophenes 10 and 11

Triethylamine (0.1 mmol) was added to a solution of the propargyl sulphoxide **9** (1 mmol) in anhydrous toluene (15 mL) at room temperature. The reaction mixture was stirred at reflux temperature for 5 h. Then, the solvent was removed under reduced pressure and the residue purified by silica gel column chromatography.

[2-(1,3-Dioxolan-2-yl)phenyl]-(2,3-dihydro-5-nitro[1]benzothien-3-yl)methanone (10a). Eluent for column chromatography: hexane/ethyl acetate (7:3 v/v); yield 41%; 0.15 g; yellow oil; IR (Neat): ν = 1698 (s), 1578 (s), 1513 (vs), 1336 (vs), 1086 (s), 909 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.74 (1H, dd, *J* = 8.8, 11.2 Hz), 3.84 (1H, dd, *J* = 5.6, 7.6 Hz), 3.88-3.98 (4H, m), 5.05 (1H, dd, *J* = 6.0, 8.8 Hz), 6.17 (1H, s), 7.29 (1H, d, *J* = 8.4 Hz), 7.37 (1H, dd, *J* = 1.2, 7.6 Hz), 7.45 (1H, td, *J* = 1.6, 7.6 Hz), 7.53 (1H, td, *J* = 1.6, 7.6 Hz), 7.68 (1H, dd, *J* = 1.2, 7.6 Hz), 7.82 (1H, dd, *J* = 1.2, 2.4 Hz), 8.03 (1H, ddd, *J* = 0.8, 2.4, 8.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.7, 58.1, 65.0, 65.2, 101.3, 121.4, 121.9, 124.2, 126.9, 127.4, 128.9, 131.2, 137.2 (s), 137.5 (s), 138.7 (s), 145.1 (s), 152.4 (s), 201.4 (s) ppm; HRMS (ESI): *m/z* calcd for $C_{18}H_{16}NO_5S$ $[M+H]^+$ 358.0744; found 358.0743.

"[2-(1,3-Dioxolan-2-yl)phenyl]-(5-nitro[1]benzothien-3-yl)methanone (11a). Eluent for column chromatography: hexane/ethyl acetate (7:3 v/v); yield 13%; 0.04 g; yellow oil; IR (Neat): ν = 1653 (m), 1517 (vs), 1342 (vs), 1234 (m), 1101 (m), 1072 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.89-3.93 (4H, m), 6.06 (1H, s), 7.48-7.51 (2H, m), 7.58 (1H, td, *J* = 2.1, 6.9 Hz), 7.74 (1H, d, *J* = 8.1 Hz), 7.99-8.02 (2H, m), 8.32 (1H, dd, *J* = 2.1, 8.7 Hz), 9.67 (1H, d, *J* = 2.1 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 65.3, 101.4, 120.1, 121.6, 122.9, 127.4, 128.0, 128.7, 130.6, 136.5 (s), 136.8 (s), 136.9 (s), 138.7 (s), 142.8, 144.5 (s), 146.8 (s), 191.2 (s) ppm; HRMS (ESI): *m/z* calcd for $C_{18}H_{14}NO_5S$ $[M+H]^+$ 356.0587; found 356.0592.

([2-(1,3-Dioxolan-2-yl)phenyl]-(5-nitro[1]benzothien-3-yl)methanone (10b). Eluent for column chromatography: hexane/ethyl acetate (7:3 v/v); yield 43%; 0.15 g; yellow oil; IR (Neat): ν = 1697 (s), 1597 (m), 1577 (m), 1514 (vs), 1336 (vs), 1265 (m) cm $^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.26 (3H, s), 3.33 (3H, s), 3.73 (1H, dd, *J* = 8.8, 11.6 Hz), 3.92 (1H, dd, *J* = 5.2, 11.6 Hz), 5.14 (1H, dd, *J* = 5.2, 8.8 Hz), 5.56 (1H, s), 7.28 (1H, d, *J* = 8.4 Hz), 7.30 (1H, d, *J* = 6.4 Hz), 7.42 (1H, td, *J* = 0.9, 7.2 Hz), 7.51 (1H, td, *J* = 0.8, 7.2 Hz), 7.59 (1H, dd, *J* = 0.4, 7.6 Hz), 7.77 (1H, d, *J* = 2.4 Hz), 8.02 (1H, dd, *J* = 2.4, 8.4 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.4, 54.0, 54.3, 58.2, 102.4, 121.4, 121.8, 124.1, 127.2, 127.8, 128.6, 130.8, 136.7 (s), 137.5 (s), 138.7 (s), 145.0 (s), 152.4 (s), 201.7 (s) ppm; HRMS (ESI): *m/z* calcd for $C_{18}H_{17}NaNO_5S$ $[M+Na]^+$ 382.0720; found 382.0720.

[2-(Dimethoxymethyl)phenyl]-(5-nitro[1]benzothien-3-yl)methanone (11b). Eluent for column chromatography: hexane/ethyl acetate (7:3 v/v); yield 13%; 0.04 g; yellow oil; IR (Neat): ν = 1740 (vs), 1521 (w), 1373 (m), 1242 (vs), 1047 (s) cm $^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.23 (6H, s), 5.63 (1H, s), 7.41-7.47 (2H, m), 7.55 (1H, td, *J* = 1.6, 7.2 Hz), 7.73 (1H, d, *J* = 7.6 Hz), 7.97 (1H, s), 8.01 (1H, d, *J* = 8.8 Hz), 8.32 (1H, dd, *J* = 2.4, 8.8 Hz), 9.67 (1H, d, *J* = 2.4 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.6, 101.1, 120.2, 121.6, 123.0, 127.3, 127.8, 128.2, 130.3, 136.5 (s), 136.9 (s), 137.1 (s), 138.7 (s), 142.1, 145.6 (s), 146.9 (s), 191.6 (s) ppm; HRMS (ESI): *m/z* calcd for $C_{18}H_{15}NaNO_5S$ $[M+Na]^+$ 380.0563; found 380.0564.

Acknowledgements

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