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A novel modification of the Ritter reaction: stereoselective synthesis of bridgehead-fused Δ^2-norbornanethiazolines from thiocamphor and thiofenchone

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Abstract—An easy two-step route for the stereoselective synthesis of novel bridgehead-fused norbornanethiazolines from readily available natural camphor and fenchone is described. The key step of the synthetic route is the highly stereoselective trapping of 1-(trifluoromethylsulfonylthio)-2-norbornyl cations by nitriles followed by intramolecular cyclization, which constitutes a new modification of the Ritter reaction.

1. Introduction

Chiral 2-oxazolines and bis-oxazolines have been widely applied in asymmetric synthesis as chiral auxiliary groups and ligands for metals in asymmetric catalysis.[1] In contrast, their sulfur analogues, the chiral 2-thiazolines, are much less known and only a few examples concerning their synthesis[2–4] and application as chiral ligands[2,3] have been reported in the literature. The exploration of chiral 2-thiazolines as ligands in asymmetric catalysis, and their comparison with the analogous oxazolines,[2e,3d,e] constitutes an attractive study since the electronic and steric effects resulting from the replacement of oxygen by sulfur may change the chelating behaviour of the heterocycle. However, the studies related to the ability of 2-thiazolines and their derivatives to act as ligands for metal-catalyzed asymmetric reactions are limited by difficult access to a large variety of enantiopure structures. This is probably due to the fact that the most usual sulfur-containing precursors, 2-aminothiols, are not easily available compared to the corresponding aminoalcohols. Nevertheless, since the first example published by Helmchen et al.[3a] about the use of metal-complexes of chiral bis(thiazolines) as catalysts, there has been increased interest in recent years in the synthesis and applications of this kind of S/N ligand.[2–4]

On the other hand, thiazolines constitute a family of compounds with considerable industrial interest, which have found applications in food and flavour chemistry.[5,6] Thiazoline derivatives have also attracted very significant biochemical interest, owing to the thiazoline ring being present as substructure in many biologically active compounds,[7] including natural products.[8] Some thiazoline derivatives present interesting pharmacological properties such as anti-HIV[6c] or anticancer[8e,f,9] activities and can also act as antihelmintic,[7a] antibiotic[7b] and antifungal[7a] agents. Thiazoline derivatives are also valuable precursor molecules to other functionalities.[4a,7b,c,10,11] The synthesis of 2-thiazolines is generally carried out by the condensation of 2-aminothiols with either a nitrile,[10a,12] a carboxylic acid[13] or an ester[14] as well as by intramolecular dehydration of β-hydroxythioamides under Mitsunobu conditions[15] or with the Burgess reagent[8f,h,16] among others.[2e,b] Other methods involve intramolecular cyclization of β-hydroxyamides with P_2S_5[4a] or Lawesson's reagent,[3c,d,4e,7c] the reaction of amino sugar derivatives with aryl isothiocyanates[4c] or deselenylation of thioamido selenides.[4d] However, in many cases, and particularly in those concerning the preparation of enantiopure chiral 2-thiazoline derivatives, several steps and/or drastic reaction conditions are

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generally required, such as the use of trialkylaluminium reagents.

In continuation of our studies on the synthesis and chemistry of enantiopure or enantioenriched bridgehead norbornane thioderivatives,[17–20] we have now found that the reaction of (1*R*)-(+)-thiocamphor and (1*R*)-(−)-thiofenchone with trifluoromethanesulfonic anhydride (Tf_2O) in the presence of nitriles leads, in a single step, to optically active bridgehead-fused norbornanethiazolines in moderate to good yields, short reaction times and mild conditions. Herein, we report the results.

2. Results and discussion

In previous studies we have demonstrated the efficiency of nitriles in trapping the reactive intermediate vinyl-,[21] 1-norbornyl-[22] and (trifluoromethylsulfonyloxy)carbenium cations.[23] Thus, the reaction of aliphatic and alicyclic ketones with trifluoromethanesulfonic anhydride in the presence of aliphatic or aromatic nitriles constitutes a very useful method for the preparation of functionalized pyrimidine derivatives.[23a,24] The mechanism of the reaction involves trapping of the intermediate (trifluoromethylsulfonyloxy)carbenium cations by the nitrile leading to the corresponding pyrimidines, via nitrilium ions.[23] The capture of (trifluoromethylsulfonyloxy)carbenium cations is faster than both proton elimination (leading to vinyl triflates) or Wagner–Meerwein rearrangement to 2-norbornyl-type cations, in the case of bicyclic ketones such as (±)-2-norbornanone and (±)-1-methyl-2-norbornanone.[23b] However, the trapping of the corresponding (trifluoromethylsulfonyloxy)carbenium cation generated from (1*R*)-(+)-camphor is hindered and a cascade of Wagner–Meerwein and Nametkin rearrangements, as well as 6,2-hydride shifts takes place. As a consequence, the trapping of the rearranged 2-norbornyl-type cations occurs after the racemizing 6,2-hydride shifts, with the main reaction products being racemic 1,3-difunctionalized norbornane derivatives instead of annulated pyrimidines.[23b]

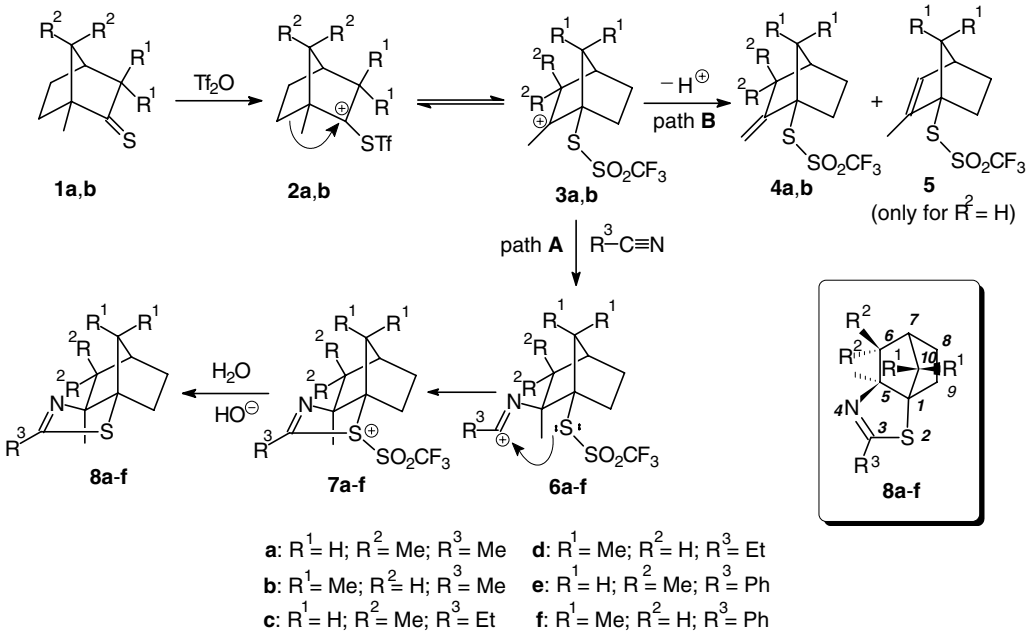
In order to explore the synthetic possibilities, which offers this Ritter-type reaction in the field of chiral norbornane sulfur derivatives, we carried out the reaction of (1*R*)-(+)-thiocamphor and (1*R*)-(−)-thiofenchone with trifluoromethanesulfonic anhydride in the presence of nitriles and found the unexpected formation of bridgehead-fused norbornanethiazolines in moderate to good yields. Our results are summarized in Scheme 1 and Table 1.

The most probable mechanism of the reaction is shown in Scheme 1. As we have previously reported, the reaction of **1** with trifluoromethanesulfonic anhydride in the presence of a base takes place with formation, as intermediates, of 2-(trifluoromethylsulfonylthio)-2-norbornyl cations **2**, which undergo a Wagner–Meerwein rearrangement leading to the 2-norbornyl-type cations **3**.[17] Elimination of a proton from **3** gives rise to the corresponding bridgehead thiotriflates **4** and **5**, which are interesting precursors to other optically active bridgehead norbornane thioderivatives.[17–20]

Table 1. Stereoselective synthesis of norbornanethiazolines

Thione	Product	Yield[a] (%)
1a	**8a**	53
	8c	48
	8e	50
1b	**8b**	74
	8d	58
	8f	49

[a] The yields are given in isolated product.



Scheme 1. Reaction of 2-norbornanethiones with Tf_2O in the presence of nitriles.

However, as we have now found, when the reaction is carried out in the presence of an excess of a nitrile and absence of a base, a mixture of bridgehead thiotriflates **4** and **5** and tricyclic bridgehead-fused norbornanethiazolines **8** is obtained, where the latter are predominant. Therefore, under the current conditions we used, two competitive reaction pathways take place. Path A involves the capture of **3** by the nitrile leading to nitrilium cations **6**. These intermediates undergo a cyclization to the *S*-(trifluoromethylsulfonyl)thiazolinium cations **7** by intramolecular nucleophilic attack of the sulfur atom (a Ritter-like reaction). Subsequent hydrolysis under basic conditions, involving nucleophilic attack at the sulfonyl sulfur atom, gives the corresponding Δ^2-thiazolines **8** in moderate to good yields (Table 1). Competitive proton elimination in cations **3** (path B) gives the corresponding bridgehead thiotriflates **4** (and **5**, in the case of thiofenchone **2b**).

These results demonstrate that (a) the Wagner–Meerwein rearrangement of 2-(trifluoromethylsulfonylthio)-2-norbornyl cations **2** is faster than their trapping by the nitrile, (b) the trapping of cations **3a** by the nitrile occurs faster than the Nametkin rearrangement and (c) this trapping is virtually 100% diastereoselective, as shown by GC/MS and ^{1}H NMR analyses of the reaction crude, which showed that only one of the two possible epimers of **8** is obtained. The absolute configuration at C(5) was unambiguously established on the basis of ^{1}H–^{13}C HMQC and selective 1D NOESY NMR experiments. The dipolar interactions are shown by arrows (see Experimental). Thus, cations **3** are attacked by the nitrile exclusively at the *exo* face giving the C(2)-*endo*-methyl substituted nitrilium ions **6**, as expected on the basis of the usual high *exo* selectivity observed for the nucleophilic attack to 2-norbornyl-type carbocations.[23b,25]

Similar to the case of (1*R*)-(+)camphor,[23b] the trapping of the corresponding (trifluoromethylsulfonylthio)carbenium ions **2** is probably hindered by the *gem*-dimethyl group. Therefore, the Wagner–Meerwein rearrangement of **2** to **3** is faster than the trapping of **2**. The capture of **3** by the nitrile, competitive with proton elimination, leads to the bridgehead-fused norbornane thiazolines **8**, which were isolated in moderate to good yields. It is interesting to note the different behaviours displayed by the norbornyl-type carbocation **3a** in comparison with its oxygenated analogue **10** generated from camphor (Scheme 2). Cation **10** undergoes a cascade of Nametkin, Wagner–Meerwein rearrangements and 6,2-hydride shifts prior to the trapping (of cation *rac*-**12**) by the nitrile affording *rac*-**13**.[23b] In contrast, the trapping of cation **3a** by the nitrile is faster than the Nametkin rearrangement, since no products arising from elimination, capture or rearrangement of **9** have been detected in the crude reaction. This different behaviour can be attributed to the different electronic effects exerted by the bridgehead electron-withdrawing substituents (–OTf and –STf). Probably, the greater $-I$ effect of trifluoromethylsulfonyloxy group, with respect to that of the trifluoromethylsulfonylthio one, destabilizes cation **10** in relation to **3a** favouring the molecular rearrangements versus the hindered trapping.

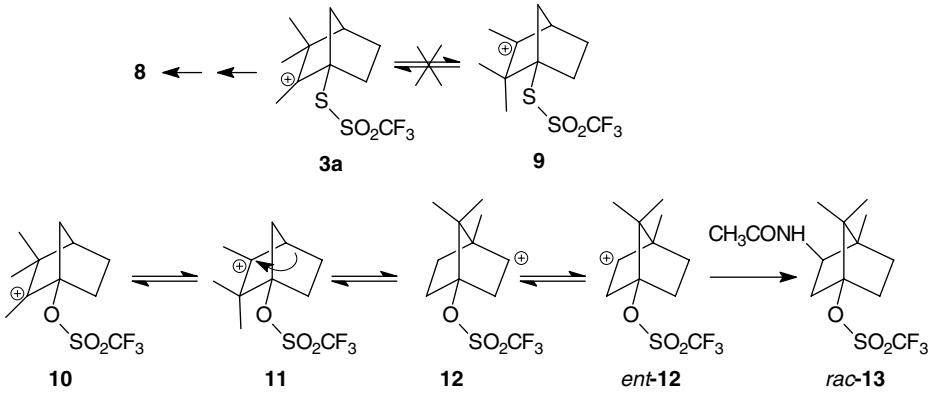
3. Conclusions

In conclusion, we have developed an efficient procedure for the stereoselective synthesis of novel optically active bridgehead norbornane-fused Δ^2-thiazolines, in only two steps, starting from commercially available (1*R*)-(+)-camphor and (1*R*)-(−)-fenchone [only a single step from commercially available (1*R*)-(+)-thiocamphor]. This procedure constitutes a novel and interesting modification of the Ritter reaction, with no precedent in the literature, and which expands the synthetic applications of nitrilium ions. The highly stereoselective trapping of 2-norbornyl-type cations **3** by the nitrile allows an easy and stereocontrolled access to a single epimer of bridgehead-fused norbornanethiazolines **8**. These compounds are intermediate precursors of other S/N bidentate ligands with norbornane framework and their possibilities in the field of asymmetric synthesis are very promising. Further work in this field is currently in progress in our laboratory.

4. Experimental

4.1. General

NMR spectra were recorded on a Bruker-AC 200 (200 MHz for ^{1}H and 50 MHz for ^{13}C) with TMS as the internal standard; *J* values are given in hertz. IR spectra were recorded on a Shimadzu FTIR spectrometer. Mass



Scheme 2. Different evolution pathways of cations **3a** and **10**.

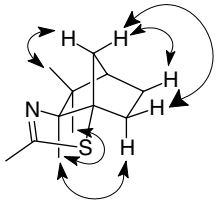
spectra were recorded on a GC–MS Shimadzu QP5000 (70 eV) mass spectrometer. For HRMS measurements, a VG Autospec was used. For gas chromatography, a Shimadzu 17 AAF chromatograph equipped with a capillary SGL-1 column was used. Optical rotation data were recorded on a Perkin–Elmer 241 polarimeter; concentrations are given as g/100 mL of the solvent.

4.2. Typical procedure for the synthesis of norbornane-thiazolines 8

To a stirred solution, cooled at 0 °C, of 5.95 mmol of (1*R*)-1,7,7-trimethylbicyclo[2.2.1]heptane-2-thione or (1*R*)-1,3,3-trimethylbicyclo[2.2.1]heptane-2-thione in 10.0 mL of the corresponding nitrile (1.0 mL in the case of benzonitrile) was added trifluoromethanesulfonic anhydride (5.95 mmol). The reaction was monitorized by GC/MS. After stirring for 1 h, the reaction mixture was carefully quenched with the saturated aqueous solution of Na_2CO_3 and extracted with CH_2Cl_2 (3×20 mL). The organic phase was extracted with 20% HCl (5×20 mL) and washed with CH_2Cl_2. Solid K_2CO_3 was slowly added in small portions to the stirred aqueous extract until basic pH. The product was then extracted with Et_2O (5×20 mL) and the combined extracts were dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure to afford the pure thiazoline as a pale yellow oil.

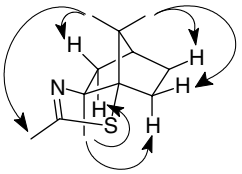
4.3. (1*R*,5*S*,7*R*)-3,5,6,6-Tetramethyl-2-thia-4-azatricyclo [5.2.1.0^{1,5}]dec-3-ene 8a

Yield 53%. $[\alpha]_D^{20} = +116.6$ (*c* 0.84, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16 (s, 3H), 2.02–1.66 (m, 5H), 1.63–1.41 (m, 2H), 1.11 (s, 3H), 1.09 (s, 3H), 0.92 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.82, 89.13, 70.29, 46.20, 43.94, 43.26, 27.18, 24.86, 23.53, 22.41, 21.42, 16.16 ppm. FTIR (film) ν 2966, 2926, 1615, 1466, 1435, 1369, 1250, 1217 cm^{-1}. MS *m*/*z* (%) 209 ($M^{+\cdot}$, 27), 194 (5), 176 (3), 168 (12), 153 (12), 140 (12), 139 (12), 127 (48), 126 (100), 112 (22), 111 (20), 91 (14), 85 (14), 79 (11), 69 (26), 59 (20), 55 (18), 53 (13), 45 (11), 42 (14), 41 (68). HRMS (EI) found: $M^{+\cdot}$, 209.1236. $C_{12}H_{19}NS$ requires: 209.1238.



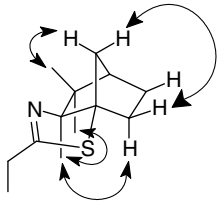
4.4. (1*R*,5*S*,7*S*)-3,5,10,10-Tetramethyl-2-thia-4-azatricyclo [5.2.1.0^{1,5}]dec-3-ene 8b

Yield 74%. $[\alpha]_D^{20} = +113.6$ (*c* 0.72, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.53 (dm, $J = 12.7$ Hz, 1H), 2.14 (s, 3H), 2.08–1.73 (m, 4H), 1.54 (d, $J = 12.7$ Hz, 1H), 1.40–1.22 (m, 1H), 1.13 (s, 3H), 0.91 (s, 3H), 0.83 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.52, 86.20, 74.20, 51.22, 43.55, 41.56, 26.12, 24.42, 23.49, 21.09, 20.88, 19.83 ppm. FTIR (CCl_4) ν 2959, 2924, 2343, 1616, 1549, 1458, 1367, 1248 cm^{-1}. MS *m*/*z* (%) 209 ($M^{+\cdot}$, 20), 194 (3), 176 (3), 168 (7), 153 (5), 140 (10), 139 (9), 127 (48), 126 (100), 112 (7), 111 (6), 91 (11), 81 (13), 59 (14), 55 (19), 42 (28), 41 (37). HRMS (EI) found: $M^{+\cdot}$, 209.1246. $C_{12}H_{19}NS$ requires: 209.1238.



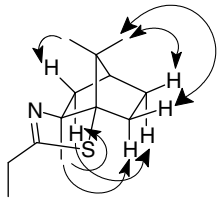
4.5. (1*R*,5*S*,7*R*)-3-Ethyl-5,6,6-trimethyl-2-thia-4-azatricyclo [5.2.1.0^{1,5}]dec-3-ene 8c

Yield 48%. $[\alpha]_D^{20} = +86.8$ (*c* 0.58, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (c, $J = 7.6$ Hz, 2H), 1.86 (dm, $J = 9.8$ Hz, 1H), 1.83–1.64 (m, 4H), 1.63–1.47 (m, 1H), 1.46 (dd, $J = 9.8$; 1.7 Hz, 1H), 1.16 (t, $J = 7.6$ Hz, 3H), 1.10 (s, 6H), 0.91 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.78, 88.77, 69.54, 46.33, 44.12, 43.47, 28.99, 27.24, 25.05, 23.72, 22.54, 16.27, 12.17 ppm. FTIR (CCl_4) ν 2968, 2937, 1616, 1458 cm^{-1}. MS *m*/*z* (%) 223 ($M^{+\cdot}$, 33), 208 (7), 168 (19), 154 (14), 153 (18), 141 (43), 140 (100), 126 (16), 125 (38), 69 (29), 55 (19), 41 (79). HRMS (EI) found: $M^{+\cdot}$, 223.1403. $C_{13}H_{21}NS$ requires: 223.1395.



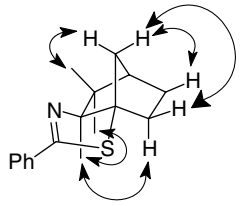
4.6. (1*R*,5*S*,7*S*)-3-Ethyl-5,10,10-trimethyl-2-thia-4-azatricyclo [5.2.1.0^{1,5}]dec-3-ene 8d

Yield 58%. $[\alpha]_D^{20} = +121.6$ (*c* 0.82, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (dm, $J = 12.7$ Hz, 1H), 2.35 (c, $J = 7.6$ Hz, 2H), 2.01–1.65 (m, 4H), 1.47 (d, $J = 12.7$ Hz, 1H), 1.32–1.12 (m, 1H), 1.10 (t, $J = 7.6$ Hz, 3H), 1.04 (s, 3H), 0.83 (s, 3H), 0.75 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.22, 85.82, 72.96, 50.99, 43.49, 41.49, 28.54, 26.00, 24.44, 23.48, 21.05, 19.74, 11.84 ppm. FTIR (CCl_4) ν 2974, 2939, 1614, 1458, 1190 cm^{-1}. MS *m*/*z* (%) 223 ($M^{+\cdot}$, 17), 208 (3), 190 (3), 180 (2), 168 (9), 154 (11), 153 (11), 141 (40), 140 (100), 135 (10), 125 (11), 112 (10), 91 (12), 81 (15), 59 (8), 56 (19), 55 (18), 41 (40). HRMS (EI) found: $M^{+\cdot}$, 223.1389. $C_{13}H_{21}NS$ requires: 223.1395.



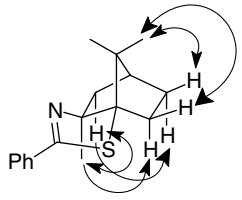
4.7. (1*R*,5*S*,7*R*)-3-Phenyl-5,6,6-trimethyl-2-thia-4-azatricyclo [5.2.1.0^{1,5}]dec-3-ene 8e

Yield 50%. $[\alpha]_D^{20} = +35.3$ (*c* 0.73, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.75 (m, 2H), 7.43–7.31 (m, 3H), 2.01–1.70 (m, 5H), 1.69–1.20 (m, 2H), 1.18 (s, 3H), 1.16 (s, 3H), 1.01 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.74, 134.89, 130.51, 128.26, 127.85, 89.65, 69.31, 46.37, 44.67, 43.46, 27.34, 25.15, 23.77, 22.65, 16.07 ppm. FTIR (CCl_4) *v* 3028, 2966, 2939, 1591, 1576, 1446 cm^{-1}. MS *m*/*z* (%) 271 ($M^{+\cdot}$, 16), 256 (3), 238 (4), 202 (15), 189 (34), 188 (100), 168 (5), 153 (8), 125 (18), 121 (17), 104 (23), 91 (14), 77 (20), 69 (24), 59 (14), 55 (15), 53 (19), 41 (97). HRMS (EI) found: $M^{+\cdot}$, 271.1389. $C_{17}H_{21}NS$ requires: 271.1395.



4.8. (1*R*,5*S*,7*S*)-3-Phenyl-5,10,10-trimethyl-2-thia-4-azatricyclo [5.2.1.0^{1,5}]dec-3-ene 8f

Yield 49%. $[\alpha]_D^{20} = +118.8$ (*c* 1.91, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85–7.77 (m, 2H), 7.48–7.30 (m, 3H), 2.68 (d, $J = 12.7$ Hz, 1H), 2.17–1.98 (m, 1H), 1.94–1.75 (m, 3H), 1.66 (d, $J = 12.7$ Hz, 1H), 1.40–1.22 (m, 1H), 1.23 (s, 3H), 0.95 (s, 3H), 0.84 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.80, 134.31, 130.60, 128.23, 127.83, 86.67, 72.75, 51.41, 43.92, 41.54, 26.12, 24.50, 23.27, 21.05, 19.76 ppm. FTIR (CCl_4) *v* 3028, 2993, 2939, 1591, 1570, 1450, 1389, 1254 cm^{-1}. MS *m*/*z* (%) 271 ($M^{+\cdot}$, 20), 256 (5), 238 (4), 202 (15), 189 (31), 188 (100), 168 (6), 153 (4), 125 (7), 104 (20), 91 (8), 77 (11), 59 (7), 55 (12), 41 (29). HRMS (EI) found: $M^{+\cdot}$, 271.1391. $C_{17}H_{21}NS$ requires: 271.1395.



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