Journal of Fluorine Chemistry 131 (2010) 852–855

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

1-Bromo-2-trifluoroacetylcyclobutenes as novel building blocks for the construction of trifluoromethyl substituted heterocycles. Part 2: Synthesis of trifluoromethyl substituted thiophenes, condensed with cyclobutene moieties

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ARTICLE INFO

Article history:
Received 1 April 2010
Received in revised form 19 April 2010
Accepted 20 April 2010
Available online 28 April 2010

Keywords:
1-Bromo-2-trifluoroacetylcyclobutenes
Mercaptoacetonitrile
Lithium 2,2,6,6-tetramethylpiperidide
Thiophenes

ABSTRACT

This paper describes a novel synthetic approach to 2-cyano-3-trifluoromethylthiophenes fused with cyclobutene rings with variable spiro conjunctions. The reaction of substituted 1-bromo-2-trifluoroacetylcyclobutenes with mercaptoacetonitrile results in the substitution of bromine with S-center to afford the corresponding nitriles in high yields, which form the target thiophenes by subsequent treatment of lithium 2,2,6,6-tetramethylpiperidide and acetic anhydride.

1. Introduction

Development of fluorine-containing building blocks for the construction of various types of fluorinated heterocycles condensed with strained carbocyclic moieties is a novel perspective challenge in organic synthesis. Although the construction of substituted trifluoromethylated thiophenes via appropriate acyclic compounds has been described in literature [1–3], the general approach for the synthesis of trifluoromethylated thiophenes condensed with variable cyclobutene skeletons became unknown until now. It should be specially stressed that cyclobutarenes represent relatively new and very perspective class of strained bicyclic structures [4]. In spite of vigorous growth of the number of publications dealing with these compounds there are only few examples of trifluoromethylated cyclobutarenes [5,6] and to the best of our knowledge there are no examples of cyclobutarenes, containing trifluoromethylated heterocyclic moieties. Recently we developed the unusual [2 + 2]-cycloaddition reactions of 1-trifluoroacetyl-2-bromoacetylene with simple alkenes to afford substituted 1-bromo-2-trifluoroacetylcyclobutenes **1a–e** [7,8] and Diels–Alder reaction giving norbornene **1f** [9,10] (Fig. 1).

In the first part of this series we have illustrated the utility of these compounds for the preparation of 5-(trifluoromethyl)-2(5H)-furanones, condensed with cyclobutene rings [11]. Herein, we report the general approach for the synthesis of cyclobutarenes, containing trifluoromethylated thiophene moieties, using **1a–f** as the parent compounds.

2. Results and discussion

The conventional construction of thiophenes via β-halogeno-α,β-unsaturated aldehydes and ketones [12] or conjugated alkynylketones [2] include their reactions with esters of thioglykolic acid followed by intramolecular Knoevenagel condensation, induced by various basic reagents. Studying this approach towards compounds **1a–f** we have found that **1a** reacts with methylthioglycolate in the presence of pyridine in very mild conditions to afford derivative **2** in a high yield (Scheme 1).

Unfortunately, all our attempts to carry out an intramolecular Knoevenagel condensation of derivative **2** leading to the corresponding cyclobutarene were unsuccessful, although we have tested a variety of bases or their combination with dehydration agents. For example, an employment of combination of Cs_2CO_3–$MgSO_4$ in methanol, which has been used in the synthesis of trifluoromethylated thiophenes [2], in our case, gave rise to a complex mixture of products. In our point of view this failure can be explained by competitive deprotonation of CH_2-group in cyclobutene moiety since the allylic carbanion formed should be effectively stabilized by trifluoroacetyl substituent. According to the literature data [1] the other probable complication consists in intramolecular Michael addition of carbanion stabilized by sulfur and ester groups to the activated C=C-bond.

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doi:10.1016/j.jfluchem.2010.04.007

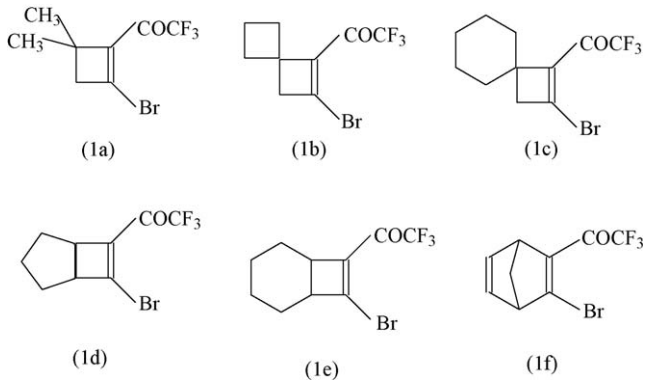


Fig. 1. The starting [2+2]-cycloadducts.

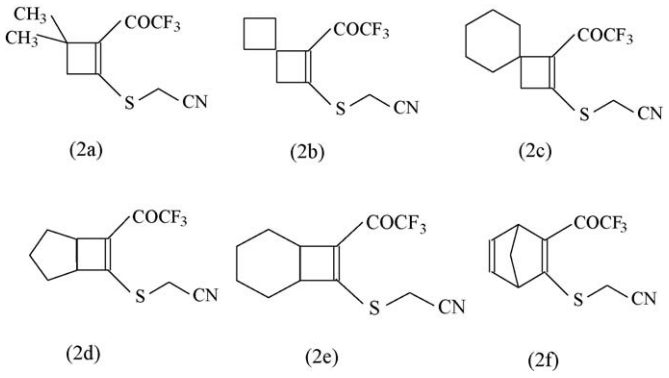
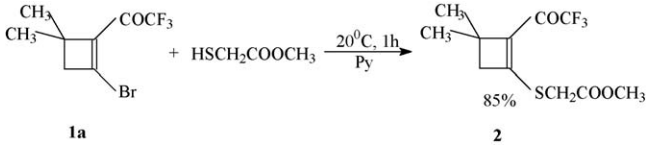


Fig. 2. The starting nitriles for cyclization.

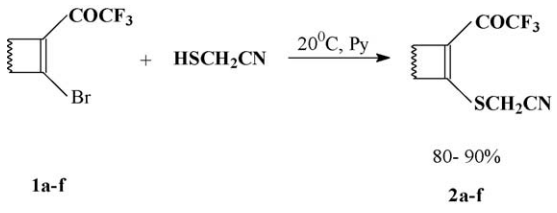
In order to overcome these difficulties it seemed reasonable to induce the regioselective and irreversible proton abstraction from SCH_2 group. It is well-known that ethylacetate and acetonitrile have approximately the same C–H acidity, however, being in cooperation with other anion stabilized function, cyano group exhibits distinctly more stabilization ability than corresponding ester group [13]. The other important feature is that the cyano group is a very compact and possesses negligible steric hindrances. Taking these facts into account we decided to study the interactions of cycloadducts **1a–f** with a relatively available mercaptoacetonitrile [14]. It was found that these processes occur nearly at the same conditions that those with methylthioglycolate (Scheme 2). Compound **1f** appeared to be most active while cycloadducts **1d**,**e** reacted somewhat slower.

Using this method the following nitriles **2a–f** have been obtained (Fig. 2).

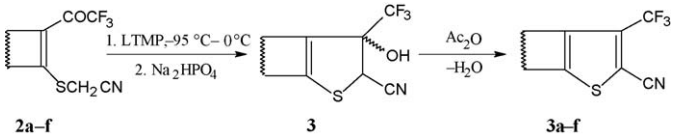
Since the acidic CH_2-group of cyclobutene rings in compounds **2a–c** and CH-group in compounds **2d**,**e** are much more steric hindered than the corresponding SCH_2CN group, in order to achieve the selective deprotonation of the latter and to avoid the nucleophilic addition of the base to the very active carbonyl function it seemed reasonable to use sterically hindered base. As such a base we have chosen lithium 2,2,6,6-tetramethylpiperidide (LTMP) which is known to be almost devoid of nucleophilic properties. According to this idea after the carbanion formation the carbonyl function should immediately play a role of internal electrophilic trap. Indeed, it was found that the addition of nitriles **2a–f** to the solution of LTMP in THF at −100 °C followed by the acidification with saturated aqueous solution of NaH_2PO_4 gives



Scheme 1. Reaction of **1a** with methylthioglycolate.



Scheme 2. Reaction of mercaptoacetonitrile with starting [2+2]-cycloadducts **1a-f**.



Scheme 3. The synthesis of condensed thiophenes **3a-f**.

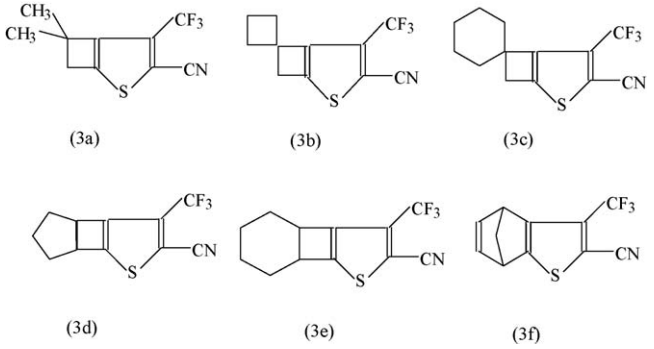


Fig. 3. The target condensed thiophenes.

rise to a mixture of aldol condensation products **3** which do not undergo instantaneous dehydration. The acidification of the reaction mixture with the strong acids resulted in the excessive formation of tarry materials. The aldols mixture has not been closely studied and separated, however treating it by an excess of acetic anhydride in the presence of 4-dimethylaminopyridine overnight we have obtained the corresponding thiophenes **3a–f** in preparative yields (Scheme 3).

Using this method the following thiophenes **3a–f** have been obtained (Fig. 3).

Since the halogenated trifluoroacetylacetylenes do easily form [2 + 2]-cycloadducts with various alkenes and cyclic vinyl ethers as well as Diels–Alder adducts with conjugated (including heterocyclic) dienes, it should be expected, that this approach will appear rather useful and general for the preparation of trifluoromethylated thiophenes fused with cyclobutene rings with variable bicyclic conjunctions. Apparently such structures are of interest for biochemists and are useful intermediates for the further diverse transformations.

3. Conclusion

In summary we have elaborated a new general method for the construction of novel cyclobutarenes, containing trifluoromethy-

lated thiophenes fused with the strained cyclobutene rings with variable spiro junctions. This approach includes the reaction of mercaptoacetonitrile with the available [2 + 2]-cycloadducts **1** formed by the addition of halogenated trifluoroacetylacetylanes to simple alkenes. The resulting nitriles **2a–f** by treatment with lithium 2,2,6,6-tetramethylpiperidide undergo intramolecular aldol condensation followed by acetic anhydride induced aromatization.

4. Experimental

Cycloadducts **1a–f** have been prepared according to described procedures [7–10]. The synthesis of **2a–f** and manipulations with BuLi and LTMP were carried out in argon atmosphere. Mercaptoacetonitrile has been prepared from chloroacetonitrile and sodium hydrosulfide [14]. In order to separate the reagent from stabilizer (H_3PO_4) it was distilled to the cold receiver and used without delay. The solution of mercaptoacetonitrile in CH_2Cl_2 was also used immediately after preparation. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on «Bruker AMX 400» spectrometer at 400 and 100 MHz respectively, chemical shifts are reported in ppm relative to 0 for TMS. IR spectra were recorded on «Bruker IFS 25» spectrometer and are reported in terms of frequency of absorption (cm^{-1}).

4.1. General procedure for the preparation of compounds 2, 2a–f

To the stirred at −10 °C solution one of the compounds **1a–f** (10 mmol) in dry CH_2Cl_2 (40 mL) pyridine (0.78 g, 10 mmol) was added after which the solution of methylthioglycolate (1.06 g, 10 mmol) or mercaptoacetonitrile (0.73 g, 10 mmol) in CH_2Cl_2 (20 mL) was added dropwise. The resulting solution was allowed to warm to ambient temperature and then was additionally stirred for 2 h (preparation of **2**, **2a–c**, **2f**) or 4 h (preparation of **2d**, **e**). The most part of solvent was removed in vacuum and the residue was diluted with THF (20 mL). The pyridinium salt was filtered off after which the solution was concentrated in vacuum and the residue was subjected to distillation (**2**, **2a**) or column chromatography (**2b–f**) (silica gel, hexane/AcOEt = 4:1).

4.1.1. Methyl {[3,3-dimethyl-2-(trifluoroacetyl)cyclobut-1-en-1-yl]thio}acetate (2)

Yellowish oil, yield 2.40 g (85%), bp 97–98 °C (1 Torr). IR (film) ν: 2999, 1745, 1704, 1602, 1270, 1233, 1168 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.38 (6H, s, $2CH_3$), 2.66 (2H, s, $CH_2C{=}C$), 3.59 (2H, s, CH_2S), 3.78 (3H, s, CH_3O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.3 ($2CH_3$), 41.9 (C–C=C), 50.9 (CH_2–C=C), 54.0 (CH_2S), 68.3 (CH_3O), 116.3 (q, J_{CF} = 283 Hz, CF_3), 140.6, 144.6 (C=C), 175.2 (q, J_{CF} = 37 Hz, $COCF_3$), 185.0 (COO); Anal. Calcd. for $C_{11}H_{13}F_3O_2S$: C, 46.8; H, 4.6; F, 20.2. Found: C, 46.7; H, 4.7; F, 20.3.

4.1.2. {[3,3-Dimethyl-2-(trifluoroacetyl)cyclobut-1-en-1-yl]thio}acetonitrile (2a)

Yellowish oil, yield 2.07 g (83%), bp 104–105 °C (1 Torr). IR (film) ν: 3000, 2245, 1705, 1600, 1277, 1239, 1168 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.40 (6H, s, $2CH_3$), 2.69 (2H, s, $CH_2C{=}C$), 3.74 (2H, s, CH_2S); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.1 ($2CH_3$), 25.8 (CH_2S), 42.2 (C–C=C), 51.0 (CH_2–C=C), 116.8 (CN), 117.7 (q, J_{CF} = 287 Hz, CF_3), 141.3, 147.6 (C=C), 177.9 (q, J_{CF} = 37 Hz, $COCF_3$); Anal. Calcd. for $C_{10}H_{10}F_3NOS$: C, 48.2; H, 4.0; F, 22.9; N, 5.6. Found: C, 48.3; H, 4.0; F, 22.7; N, 5.4.

4.1.3. {[1-(Trifluoroacetyl)spiro[3.3]hept-1-en-2-yl]thio}acetonitrile (2b)

Yellowish oil, yield 2.06 g (79%), the substance was purified by column chromatography. IR (film) ν: 3010, 2243, 1709, 1600, 1275, 1239, 1177 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.20–2.38 (4H, m, 4C–H in cyclobutane), 2.56 (2H, dd, J = 12.7, 8.6 Hz, 2C–H in cyclobutane), 2.89 (2H, s, CH_2–C=C), 3.77 (2H, s, CH_2S); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.8, 20.3, 31.0 (($CH_2)_3$, CH_2S), 43.3 (C–C=C), 51.9 (CH_2–C=C), 117.1 (CN), 118.4 (q, J_{CF} = 287 Hz, CF_3), 141.6, 148.8 (C=C), 179.0 (q, J_{CF} = 37 Hz, $COCF_3$); Anal. Calcd. for $C_{11}H_{10}F_3NOS$: C, 50.6; H, 3.9; F, 21.8; N, 5.4. Found: C, 50.7; H, 3.7; F, 21.7; N, 5.2.

4.1.4. {[1-(Trifluoroacetyl)spiro[3.5]non-1-en-2-yl]thio}acetonitrile (2c)

Yellowish crystals, yield 2.31 g (80%), mp 33–34 °C, the substance was purified by column chromatography. IR (mineral oil) ν: 3014, 2240, 1712, 1600, 1275, 1243, 1180 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.16–1.33 (m), 1.51–1.63 (m), 1.90–1.99 (m) (totally 10H, $(CH_2)_5$), 2.68 (2H, s, CH_2–C=C), 3.70 (2H, s, CH_2S); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.3, 24.9, 25.5, 32.7 (($CH_2)_5$, CH_2S), 49.7 (C–C=C), 51.1 (CH_2–C=C), 116.4 (CN), 117.7 (q, J_{CF} = 288 Hz, CF_3), 141.1, 146.7 (C=C), 179.4 (q, J_{CF} = 37 Hz, $COCF_3$); Anal. Calcd. for $C_{13}H_{14}F_3NOS$: C, 54.0; H, 4.9; F, 19.7; N, 4.8. Found: C, 54.1; H, 4.9; F, 19.6; N, 4.7.

4.1.5. {[7-(Trifluoroacetyl)bicyclo[3.2.0]hept-6-en-6-yl]thio}acetonitrile (2d)

Yellowish oil, yield 2.24 g (82%), the substance was purified by column chromatography. IR (film) ν: 3015, 2995, 2240, 1705, 1603, 1272, 1233, 1164 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.29–1.42 (m), 1.46–1.55 (m), 1.73–1.90 (m) (totally 6H, $(CH_2)_3$), 3.42 (1H, dd, J = 6.4, 3.4 Hz, CH–C=C), 3.62 (1H, dd, J = 6.4, 3.4 Hz, CH–C=C), 3.73–3.77 (2H, m, CH_2S); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 24.4, 25.5, 25.9 (($CH_3)_3$, CH_2S), 46.7, 53.6 (CH–CH), 115.9 (CN), 117.3 (q, J_{CF} = 288 Hz, CF_3), 141.0, 149.8 (C=C), 176.7 (q, J_{CF} = 38 Hz, $COCF_3$); Anal. Calcd. for $C_{12}H_{10}F_3NOS$: C, 52.8; H, 3.7; F, 20.9; N, 5.1. Found: C, 52.9; H, 3.8; F, 20.8; N, 5.0.

4.1.6. {[8-(Trifluoroacetyl)bicyclo[4.2.0]oct-7-en-7-yl]thio}acetonitrile (2e)

Yellowish oil, yield 2.21 g (77%), the substance was purified by column chromatography. IR (film) ν: 3013, 2999, 2240, 1702, 1600, 1275, 1235, 1170 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.25–1.40 (m), 1.49–1.74 (m) (totally 8H, $-(CH_2)_4-$), 3.19 (1H, dd, J = 6.4, 4.2 Hz, –CH–CH–), 3.35 (1H, dd, J = 6.4, 4.2 Hz, –CH–CH–), 3.70–3.74 (2H, m, CH_2S); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.9, 18.4, 22.5, 23.0 (($CH_2)_4$), 25.6 (CH_2S), 41.1, 48.4 (CH–CH), 115.4 (CN), 116.6 (q, J_{CF} = 288 Hz, CF_3), 139.8, 147.5 (C=C), 175.0 (q, J_{CF} = 38 Hz, $COCF_3$); Anal. Calcd. for $C_{13}H_{12}F_3NOS$: C, 54.4; H, 4.2; F, 19.8; N, 4.9. Found: C, 54.4; H, 4.2; F, 19.7; N, 4.8.

4.1.7. {[3-(Trifluoroacetyl)bicyclo[2.2.1]hepta-2,5-dien-2-yl]thio}acetonitrile (2f)

Yellowish crystals, yield 2.33 g (90%), mp 41–42 °C, the substance was purified by column chromatography. IR (mineral oil) ν: 3004, 2240, 1700, 1608, 1370, 1268, 1230, 1170 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.20 (1H, d, J = 7.2 Hz, $-CH_2-$); 2.34 (1H, d, J = 7.2 Hz, $-CH_2-$); 3.62 (1H, s, H–C^1), 4.14 (1H, s, H–C^4), 4.20–4.24 (2H, m, CH_2S), 6.79 (1H, d, CH=CH, J = 4.9 Hz); 6.92 (1H, d, J = 4.9 Hz, CH=CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.0 (CH_2S), 32.2 (CH_2), 49.7, 53.3 (C^1, C^4), 115.6 (CN), 117.9 (q, J_{CF} = 290 Hz, CF_3), 136.1, 139.9 (CH=CH), 145.3, 169.9 (C=C), 177.4 (q, J_{CF} = 38 Hz, $COCF_3$); Anal. Calcd. for $C_{11}H_8F_3NOS$: C, 51.0; H, 3.1; F, 22.0; N, 5.4. Found: C, 51.1; H, 3.1; F, 21.8; N, 5.3.

4.2. General procedure for the preparation of thiophenes 3a–f

To a stirred at 0 °C solution of 2,2,6,6-tetramethylpiperidine (0.78 g, 5.5 mmol) in THF (40 mL) a solution of BuLi in hexane

(3.1 mL, 5 mmol of 1.6N solution) was added dropwise. After the mixture was stirred for 30 min at 0 °C, diluted with hexane (20 mL) and subsequently cooled to −100 °C, a solution of the nitrile **2a**–**f** (5 mmol) in THF (5 mL) was added over 1 min. The reaction mixture was stirred for 15 min at the same temperature, then during 30 min allowed to warm to 0 °C and subsequently was poured into the stirred saturated solution of NaH_2PO_4 (40 mL). The organic layer was separated after which an aqueous phase was extracted with ether (2 × 20 mL) and combined organic solution was dried over Na_2SO_4. The solvent was removed in vacuum and the residue was dissolved in acetic anhydride (15 mL) containing triethylamine (1.2 g, 12 mmol) and 4-dimethylaminopyridine (0.2 g, 1.6 mmol). The resulting solution was kept for 12 h at 20 °C and the most part of acetic anhydride was distilled off in vacuum. The residue was diluted with ether (50 mL), consequently washed with saturated solutions of NaH_2PO_4 (20 mL) and $NaHCO_3$ (20 mL), dried over Na_2SO_4 and after the evaporation of solvent the crude product was subjected to column chromatography (silica gel, hexane/AcOEt = 5:1) to afford thiophenes **3a**–**f**.

*4.2.1. 6,6-Dimethyl-4-(trifluoromethyl)-2-thiabicyclo[3.2.0]hepta-1(5),3-diene-3-carbonitrile (**3a**)*

Colorless oil, yield 0.65 g (56%). IR (film) ν: 3044, 3000, 2220, 1470, 1385, 1277, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.39 (6H, s, $(CH_3)_2C$), 2.73 (2H, s, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.0 ($2CH_3$), 43.8($\underline{C}(CH_3)_2$), 51.6 (CH_2), 109.4 ($\underline{C}$–CN), 112.0 (CN), 120.7 (q, J_{CF} = 274 Hz, CF_3), 128.9 (C=$\underline{C}$–S), 139.4 (C=$\underline{C}$–S), 141.6 (q, J_{CF} = 36 Hz, $\underline{C}$–CF_3); Anal. Calcd. for $C_{10}H_8F_3NS$: C, 51.9; H, 3.5; F, 24.7; N, 6.1; S, 13.9. Found: C, 52.1; H, 3.5; F, 24.5; N, 5.9; S, 13.8.

*4.2.2. 4-(Trifluoromethyl)-2-thiaspiro[bicyclo[3.2.0]heptane-6,1′-cyclobutane]-1(5),3-diene-3-carbonitrile (**3b**)*

Colorless oil, yield 0.72 g (59%). IR (film) ν: 3048, 3010, 2995, 2220, 1474, 1370, 1275, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.15–2.25 (2H, m, 2C–H in cyclobutane), 2.56–2.69 (4H, m, 4C–H in cyclobutane), 3.01 (2H, s, CH_2–Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.0, 32.2 (–$(CH_2)_3$–), 44.5($\underline{C}(CH_2)_3$), 52.8 ($\underline{C}H_2$–Ar), 109.9 ($\underline{C}$–CN), 113.7 (CN), 121.1 (q, J_{CF} = 274 Hz, CF_3), 132.7 ($\underline{C}$=C–S), 142.0 (C=$\underline{C}$–S), 144.9 (q, J_{CF} = 34 Hz, $\underline{C}$–CF_3); Anal. Calcd. for $C_{11}H_8F_3NS$: C, 54.3; H, 3.3; F, 23.4; N, 5.8; S, 13.2. Found: C, 54.5; H, 3.4; F, 23.3; N, 5.6; S, 13.0.

*4.2.3. 4-(Trifluoromethyl)-2-thiaspiro[bicyclo[3.2.0]heptane-6,1′-cyclohexane]-1(5),3-diene-3-carbonitrile (**3c**)*

Colorless crystals, yield 0.81 g (60%), mp 36–37 °C. IR (mineral oil) ν: 3044, 3005, 2998, 2220, 1470, 1377, 1260, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.19–1.35 (m), 1.50–1.63 (m), 1.86–2.00 (m) (totally 10H, $(CH_2)_5$), 2.69 (2H, s, CH_2–Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.8, 25.0, 33.1 (–$(CH_2)_5$–), 42.9($\underline{C}(CH_2)_5$), 47.7 ($\underline{C}H_2$–Ar), 109.7($\underline{C}$–CN), 112.2 (CN), 119.6 (q, J_{CF} = 274 Hz, CF_3), 128.6 ($\underline{C}$=C–S), 136.9 (C=$\underline{C}$–S), 140.9 (q, J_{CF} = 36 Hz, $\underline{C}$–CF_3); Anal. Calcd. for $C_{13}H_{12}F_3NS$: C, 57.6; H, 4.5; F, 21.0; N, 5.2; S, 11.8. Found: C, 57.6; H, 4.6; F, 20.9; N, 5.0; S, 11.7.

*4.2.4. 3-(Trifluoromethyl)-4,5,6,6a-tetrahydro-3bH-cyclopenta[3,4]cyclobuta[1,2-b]thiophene-2-carbonitrile (**3d**)*

Colorless oil, yield 0.83 g (68%). IR (film) ν: 3040, 3010, 2995, 2220, 1462, 1377, 1266, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.30–1.47 (m), 1.48–1.58 (m), 1.77–1.91 (m) (totally 6H, $(CH_2)_3$), 3.56 (1H, dd, J = 6.5, 3.3 Hz, –CH–CH–), 3.71 (1H, dd, J = 6.5, 3.3 Hz, –CH–CH–); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.8, 25.4, 26.0 (–$(CH_2)_3$–), 48.2, 55.9 (–CH–CH–), 109.5 ($\underline{C}$–CN), 112.0 (CN), 120.2 (q, J_{CF} = 272 Hz, CF_3), 129.5 ($\underline{C}$=C–S), 138.8 (C=$\underline{C}$–S), 142.7 (q, J_{CF} = 36 Hz, $\underline{C}$–CF_3); Anal. Calcd. for $C_{11}H_8F_3NS$: C, 54.3; H, 3.3; F, 23.4; N, 5.8; S, 13.2. Found: C, 54.4; H, 3.4; F, 23.5; N, 5.6; S, 13.1.

*4.2.5. 3-(Trifluoromethyl)-3b,4,5,6,7,7a-hexahydrobenzo[3,4]cyclobuta[1,2-b]thiophene-2-carbonitrile (**3e**)*

Colorless oil, yield 0.91 g (71%). IR (film) ν: 3045, 3010, 2991, 2218, 1460, 1377, 1265, 1190, 1175 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.38–1.58 (m), 1.56–2.10 (m) (totally 8H, –$(CH_2)_4$–), 3.28 (1H, dd, J = 6.8, 4.2 Hz, –CH–CH–), 3.36 (1H, dd, J = 6.8, 4.2 Hz, –CH–CH–); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 14.8, 18.4, 19.9 (–$(CH_2)_4$–), 36.8, 43.9 (–CH–CH–), 108.8 ($\underline{C}$–CN), 111.2 (CN), 119.3 (q, J_{CF} = 272 Hz, CF_3), 129.0 ($\underline{C}$=C–S), 136.9 (C=$\underline{C}$–S), 140.4 (q, J_{CF} = 36 Hz, $\underline{C}$–CF_3); Anal. Calcd. for $C_{12}H_{10}F_3NS$: C, 56.0; H, 3.9; F, 22.2; N, 5.4; S, 12.5. Found: C, 56.2; H, 4.1; F, 22.1; N, 5.3; S, 12.5.

*4.2.6. 3-(Trifluoromethyl)-4,7-dihydro-4,7-methano-1-benzothiophene-2-carbonitrile (**3f**)*

Yellowish oil, yield 0.78 g (65%). IR (film) ν: 3025, 3005, 2227, 1698, 1433, 1370, 1260, 1185 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.34 (1H, d, J = 7.5 Hz, CH_2), 2.48 (1H, d, J = 7.5 Hz, CH_2), 3.95 (1H, d, J = 1.5 Hz, H–C^1), 4.09 (1H, d, J = 1.5 Hz, H–C^4), 6.86 (1H, dd, J = 4.9, 1.5 Hz, H–C=), 6.95 (1H, dd, J = 4.9, 1.5 Hz, H–C=); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.4 (CH_2), 44.6, 45.9 (C^1, C^4), 110.3 ($\underline{C}$–CN), 113.4 (CN), 120.0 (q, J_{CF} = 274 Hz, CF_3), 136.3, 140.3 ($\underline{C}$=$\underline{C}$–S), 144.0, 146.6 (C=C); Anal. Calcd. for $C_{11}H_6F_3NS$: C, 54.8; H, 2.5; F, 23.6; N, 5.8; S, 13.3. Found: C, 54.9; H, 2.6; F, 23.5; N, 5.6; S, 13.2.

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