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Synthesis of trifluoromethylated 1,5-benzoheteroazepines

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ABSTRACT

Because of the great interest of benzoheteroazepines and trifluoromethylated compounds in medicinal chemistry, a simple strategy to synthesize trifluoromethylated 1,5-benzoheteroazepines have been described. Starting from β-trifluoromethylated enones and 1,2-diamines or 1,2-thioamines, various benzodiazepines and benzothiazepines bearing a CF_3 group have been obtained in good yields.

1. Introduction

Benzodiazepines have received much attention as an important class of *N*-heterocyclic compounds exhibiting a broad spectrum of biological and pharmacological activities, such as anti-inflammatory, anticonvulsant, antianxiety, sedative, antidepressive and hypnotic activities [1–4]. 1,5-Benzodiazepines exert a biological activity similar to well known 1,4-derivatives and their ring system has demonstrated considerable utility not only in central nervous system (CNS) drug design, as illustrated by the atypical antipsychotic Clozapine [5], but also as peptidomimetic scaffolds [6–19] and key intermediates for the preparation of other fused ring compounds [20–26].

Sulfur derivatives, namely 1,5-benzothiazepines, possess also interesting properties as illustrated by Diltiazem, a calcium-channel blocker used as antiarrhythmic [27].

It is now well admitted that the introduction of fluorinated moieties onto organic molecules brings important physico-chemical modifications which, often, allow pertinent modulations of pharmacokinetic properties of molecules. In particular, the increased lipophilicity of trifluoromethylated compounds could favor the transmembrane permeation allowing a better biodisponibility of trifluoromethylated drugs [28–33].

In this context, because of the pharmacological importance of benzodiazepines and benzothiazepines classes of compounds, it could be interesting to synthesize trifluoromethylated derivatives of such families of molecules.

2. Results and discussion

The commonly employed methods to construct the ring skeletons involve the cyclocondensation of 1,2-diamines with ketones [34–43], enones [35,44–46], β-haloketones [6–19], alkynes [47] and require the use of various catalysts.

A few years ago, we described simple methods to obtain β-trifluoromethylated enones [48,49] which constitute an interesting class of fluorinated building-blocks as starting materials for the synthesis of various fluorinated molecules [49–54]. In view of the previous methods described in literature such fluorinated enones appeared as valuable substrates to easily synthesize various 1,5-benzoheteroazepines.

Supposing that β-trifluoromethylated enones are more reactive than their hydrogenated analogs, because of the CF_3 group presence, the reaction between the *o*-phenylenediamine (**1a**) and the enone **2a** has been tested without catalyst. However, in this case no formation of the expected compound (**3aa**) has been observed. In basic conditions, the 1,4-addition of **1a** is favored but the cyclization by imine formation is unfavorable. In acidic conditions, the protonation of **1a** decreases its reactivity, in particular for the conjugated addition.

The two steps required for the formation of the diazepine ring are equilibriums between Michael/retro-Michael reaction and ketone/imine formation. Consequently, if **2a** is electrophilic

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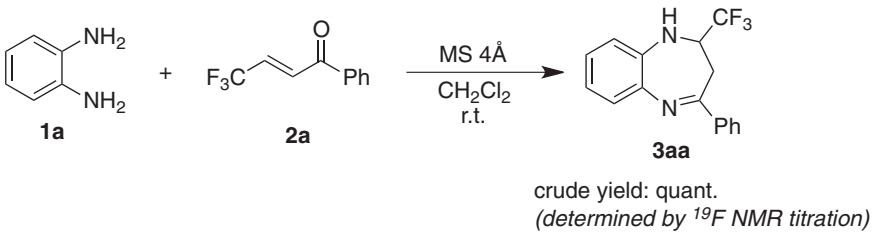

Scheme 1. Condensation of *o*-phenylenediamine with **2a**.

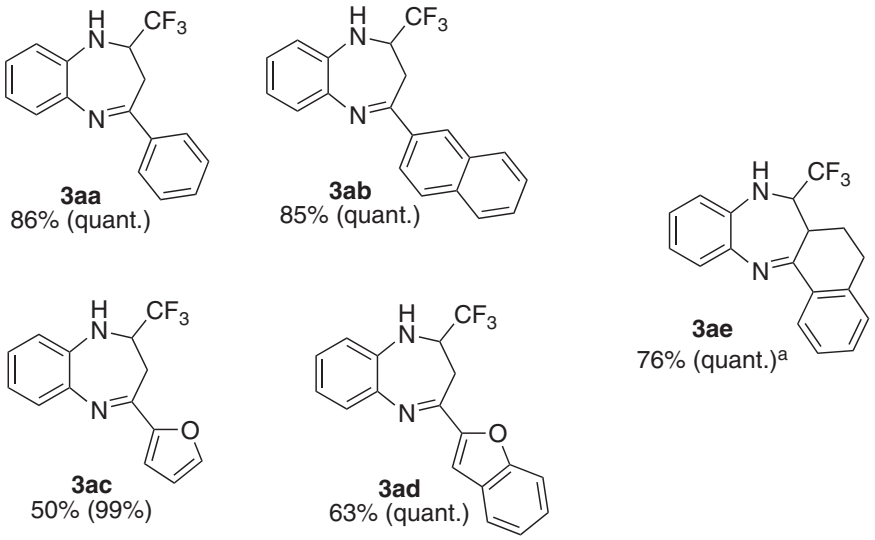

Fig. 1. Various 1,5-benzodiazepines from **1a**. (Isolated yields after recrystallization. In parentheses, crude yields determined by ^{19}F NMR titration with $PhOCF_3$ as internal standard. [a]110 °C in toluene instead of r.t. in CH_2Cl_2.)

enough to react with **1a**, these equilibriums should be simply displaced by favoring the formation of imine. In this logic, the *o*-phenylenediamine **1a** and the β-trifluoromethylated enone were mixed in presence of molecular sieves in dichloromethane. With these conditions, the expected 1,5-benzodiazepine **3aa** was quantitatively formed at room temperature in 24 h (Scheme 1).

These conditions have been extended to other β-trifluoromethylated enones (Fig. 1). After filtration and evaporation, the isolated 1,5-benzodiazepines **3** were obtained with a satisfactory purity. However, they can be further purified by recrystallization, because of their low solubility. All the expected 1,5-benzodiazepines **3** were obtained with excellent yields. The purified yields are

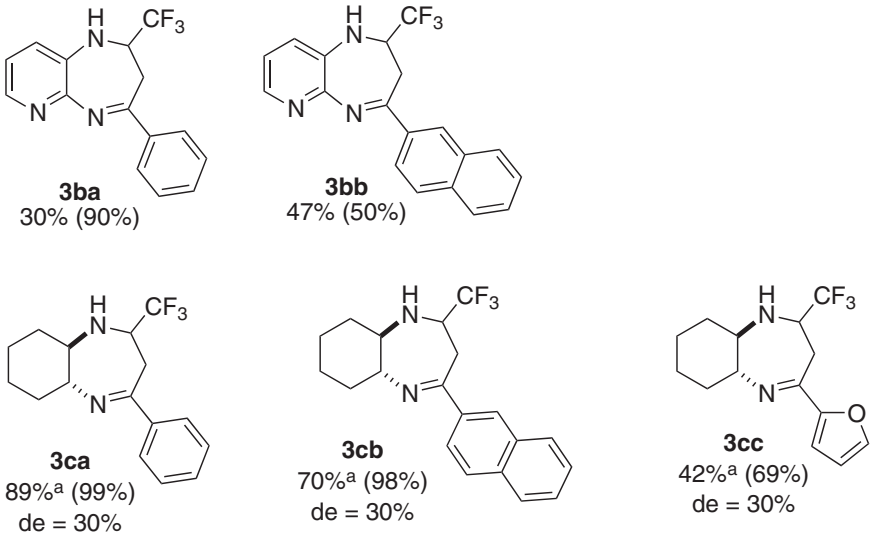

Fig. 2. Various 1,5-benzodiazepines. (Isolated yields. In parentheses, crude yields determined by ^{19}F NMR titration with $PhOCF_3$ as internal standard.) [a]purified by flash chromatography.

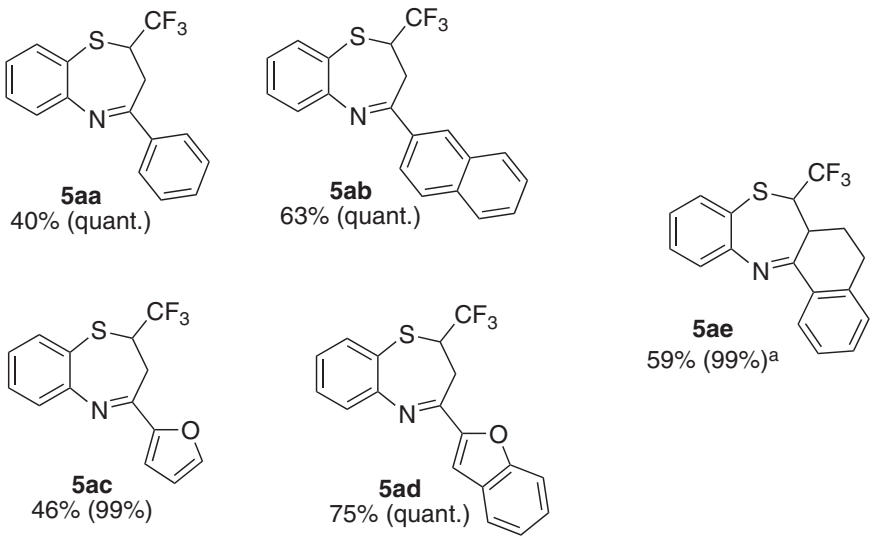

Fig. 3. Various 1,5-benzothiazepines from **4a**. (Isolated yields after recrystallization. In parentheses, crude yields determined by ^{19}F NMR titration with $PhOCF_3$ as internal standard. [a]110 °C in toluene instead of r.t. in CH_2Cl_2.)

sometimes lower than crude yields because of not optimized recrystallization conditions. In the case of the more hindered β-trifluoromethylated enone arising from tetralone (**2e**), heating at 110 °C in toluene was required to perform the reaction.

To extend the panel of the obtained 1,5-benzodiazepines, the diamines have been also diversified (Fig. 2).

Because of the lower nucleophilicity of the pyridine-2,3-diamine (**1b**) and the steric hindrance of the *trans*-cyclohexane-1,2-diamine (**1c**), the reaction mixtures were heated at 110 °C in toluene to perform the reaction. The expected 1,5-benzodiazepines **3** were then obtained with satisfactory to excellent yields. In the case of the pyridine-2,3-diamine, a good regioselectivity was observed. The strategy could be also applied to non aromatic diamines, as illustrated by obtained products **3c** by starting from the *trans*-cyclohexane-1,2-diamine. In this case a poor diastereoselectivity is observed.

Because of the interest of 1,5-benzothiazepines, the previous method has been also extended to *o*-aminothiophenol (**4a**) (Fig. 3).

Similar results than with diamines were obtained with also excellent yields. The formation of product **5ae** required, as previously, a heating to 110 °C to be formed. It should be noticed that because of the lower nucleophilicity of *o*-aminothiophenol, the reaction required 72 h, instead of 24 h for diamines, to give similar results.

3. Conclusion

In conclusion, trifluoromethylated 1,5-benzoheteroazepines can be easily synthesized starting from β-trifluoromethylated enones, following a simple process requiring only a filtration/evaporation/recrystallization sequence for purification. Such strategy should facilitate high throughput development of libraries of such benzoheteroazepines for further screenings. These results confirm also the high synthetic potential of β-trifluoromethylated enones to access to more elaborated fluorinated molecules.

4. Experimental part

Typical procedure: To a solution of 1 mmol of β-trifluoromethylated enone **2** in 2 mL of solvent (CH_2Cl_2 or toluene) was added 1 eq of diamine **1** or aminothiophenol **4** following by 1 g of 4 Å molecular sieves. The reaction mixture was stirred during 24 h or 72 h at room temperature or 110 °C. After filtration and solvent evaporation, the crude product was purified by recrystallization in CH_2Cl_2/pentane.

4.1. 4-Phenyl-2-(trifluoromethyl)-2,3-dihydro-1H-1,5-benzodiazepine (3aa)

Yellow solid. Mp 83–85 °C.

^1H NMR (300 MHz, $CDCl_3$): δ 8.03 (m, 2H), 7.48–7.55 (massif, 3H), 7.32 (dd, 1H, $^3J_{HH}$ = 7.3 Hz, $^4J_{HH}$ = 1.8 Hz), 7.16 (ddd, 1H, $^3J_{HH}$ = $^3J_{HH}$ = 7.3 Hz, $^4J_{HH}$ = 1.7 Hz), 7.10 (ddd, 1H, $^3J_{HH}$ = $^3J_{HH}$ = 7.3 Hz, $^4J_{HH}$ = 1.8 Hz), 6.92 (dd, 1H, $^3J_{HH}$ = 7.3 Hz, $^4J_{HH}$ = 1.7 Hz), 4.50 (ddq, 1H, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 4.1 Hz, $^3J_{HF}$ = 7.0 Hz), 3.72 (bs, 1H), 3.22 (dd, 1H, $^3J_{HH}$ = 4.1 Hz, $^2J_{HH}$ = 13.5 Hz), 2.97 (dd, 1H, $^2J_{HH}$ = 10.6 Hz, $^2J_{HH}$ = 13.5 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1, 141.4, 138.6, 135.8, 131.3, 129.2, 128.3, 127.4, 127.1, 125.2 (q, $^1J_{CF}$ = 285.1 Hz, CF_3), 123.8, 122.5, 67.7 (q, $^2J_{CF}$ = 28.4 Hz), 27.4 (q, $^3J_{CF}$ = 1.6 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ − 78.42 (d, $^3J_{FH}$ = 7.0 Hz).

Anal. calcd for $C_{16}H_{13}F_3N_2$: C 66.20; H 4.51; N 9.65; found: C 66.39; H 4.47; N 9.57.

4.2. 4-(2-Naphthyl)-2-(trifluoromethyl)-2,3-dihydro-1H-1,5-benzodiazepine (3ab)

Yellow solid. Mp 90–101 °C.

^1H NMR (300 MHz, $CDCl_3$): δ 8.35 (bs, 1H), 8.32 (dd, 1H, $^3J_{HH}$ = 8.6 Hz, $^4J_{HH}$ = 1.8 Hz), 7.88–8.02 (massif, 3H), 7.52–7.63 (massif, 2H), 7.38 (dd, 1H, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.7 Hz), 7.17 (ddd, 1H, $^3J_{HH}$ = 7.5 Hz, $^3J_{HH}$ = 7.3 Hz, $^4J_{HH}$ = 1.6 Hz), 7.12 (ddd, 1H, $^3J_{HH}$ = 7.3 Hz, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.7 Hz), 6.95 (dd, 1H, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.6 Hz), 4.57 (ddq, 1H, $^3J_{HH}$ = 10.7 Hz, $^3J_{HH}$ = 4.2 Hz, $^3J_{HF}$ = 6.7 Hz), 3.75 (bs, 1H), 3.38 (dd, 1H, $^3J_{HH}$ = 13.5 Hz, $^3J_{HH}$ = 4.2 Hz), 3.07 (dd, 1H, $^3J_{HH}$ = 13.5 Hz, $^3J_{HH}$ = 10.7 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 168.9, 141.5, 136.0, 135.9, 135.0, 133.5, 129.5, 129.0, 128.5, 128.2, 128.0, 127.7, 127.1, 127.0, 125.3 (q, $^1J_{CF}$ = 285.2 Hz, CF_3), 124.6, 123.9, 122.6, 67.8 (q, $^2J_{CF}$ = 28.4 Hz), 27.3.

^{19}F NMR (282 MHz, $CDCl_3$): δ − 78.22 (d, $^3J_{FH}$ = 6.8 Hz).

Anal. calcd for $C_{20}H_{15}F_3N_2$: C 70.58; H 4.44; N 8.23; found: C 70.83; H 4.18; N 7.88.

*4.3. 4-(2-Furyl)-2-(trifluoromethyl)-2,3-dihydro-1*H*-1,5-benzodiazepine (3ac)*

Yellow solid. Mp 91–96 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (dd, 1H, $^3J_{HH}$ = 1.7 Hz, $^3J_{HH}$ = 0.8 Hz), 7.32 (dd, 1H, $^4J_{HH}$ = 2.0 Hz, $^3J_{HH}$ = 7.3 Hz), 7.00–7.16 (massif, 3H), 6.89 (dd, 1H, $^4J_{HH}$ = 1.6 Hz, $^3J_{HH}$ = 7.5 Hz), 6.57 (dd, 1H, $^3J_{HH}$ = 1.7 Hz, $^3J_{HH}$ = 3.5 Hz), 4.48 (ddqd, 1H, $^3J_{H1-NH}$ = 1.7 Hz, $^3J_{HH}$ = 4.8 Hz, $^3J_{HF}$ = 6.8 Hz, $^3J_{HH}$ = 9.7 Hz), 3.72 (bs, 1H), 3.07 (dd, 1H, $^2J_{HH}$ = 13.5 Hz, $^3J_{HH}$ = 4.8 Hz), 2.89 (dd, 1H, $^2J_{HH}$ = 13.5 Hz, $^3J_{HH}$ = 9.7 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.8, 152.9, 146.0, 140.9, 136.0, 128.6, 127.0, 125.1 (q, $^1J_{CF}$ = 284.7 Hz, CF_3), 123.9, 122.5, 113.7, 112.8, 67.6 (q, $^2J_{CF}$ = 28.5 Hz), 27.4 (q, $^3J_{CF}$ = 1.8 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ – 78.58 (d, $^3J_{FH}$ = 6.8 Hz).

Anal. calcd for $C_{14}H_{11}F_3N_2O$: C 60.00; H 3.96; N 10.00; found: C 60.31; H 4.19; N 10.08.

*4.4. 4-(1-Benzofuran-2-yl)-2-(trifluoromethyl)-2,3-dihydro-1*H*-1,5-benzodiazepine (3ad)*

Yellow solid. Mp 109–111 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61–7.71 (massif, 2H), 7.39–7.45 (massif, 2H), 7.38 (s, 1H), 7.30 (m, 1H), 7.07–7.18 (massif, 2H), 6.92 (m, 1H), 4.54 (ddq, 1H, $^3J_{HH}$ = 4.7 Hz, $^3J_{HH}$ = 9.5 Hz, $^3J_{HF}$ = 6.9 Hz), 3.80 (bs, 1H), 3.16 (dd, 1H, $^2J_{HH}$ = 13.6 Hz, $^3J_{HH}$ = 4.7 Hz), 2.99 (dd, 1H, $^3J_{HH}$ = 13.6 Hz, $^3J_{HH}$ = 9.5 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 157.3, 156.4, 154.0, 140.7, 136.1, 129.0, 128.5, 127.5, 127.2, 125.1 (q, $^1J_{CF}$ = 284.7 Hz, CF_3), 124.0, 123.9, 122.5, 122.5, 110.0, 67.8 (q, $^2J_{CF}$ = 28.6 Hz), 27.7 (q, $^3J_{CF}$ = 1.8 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ – 78.47 (d, $^3J_{FH}$ = 6.9 Hz).

Anal. calcd for $C_{18}H_{13}F_3N_2O$: C 65.45; H 3.97; N 8.48; found: C 65.58; H 3.78; N 8.32.

*4.5. 7-(Trifluoromethyl)-6.6a,7.8-tetrahydro-5*H*-naphtho[1,2-b][1,5]benzodiazepine (3ae)*

Yellow solid. Mp 98–102 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.42 (dd, 1H, *J* = 7.7 Hz, *J* = 1.7 Hz), 7.15–7.47 (massif, 5H), 7.07 (td, 1H, *J* = 7.5 Hz, *J* = 1.6 Hz), 6.93 (dd, 1H, *J* = 7.9 Hz, *J* = 1.5 Hz), 4.35 (dq, 1H, $^3J_{HH}$ = 11.5 Hz, $^3J_{HF}$ = 7.0 Hz), 3.70 (s, 1H), 3.30 (dt, 1H, $^3J_{HH}$ = 11.5 Hz, $^3J_{HH}$ = 4.6 Hz), 3.02 (ddd large, 1H, $^2J_{HH}$ = 16.6 Hz, $^3J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 7.5 Hz H-5A), 2.81 (dt, 1H, $^2J_{HH}$ = 16.6 Hz, $^3J_{HH}$ = 4.4 Hz), 2.10 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1, 142.8, 140.7, 135.8, 133.2, 131.3, 128.9, 127.4, 127.24, 127.21, 126.3, 125.4 (q, $^1J_{CF}$ = 288.2 Hz, CF_3), 124.7, 123.2, 68.6 (q, $^2J_{CF}$ = 25.6 Hz), 36.2, 26.0, 24.2 (q, $^4J_{CF}$ = 2.2 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ – 73.24 (d, $^3J_{FH}$ = 7.0 Hz).

Anal. calcd for $C_{18}H_{15}F_3N_2$: C 68.35; H 4.78; N 8.86; found: C 68.08; H 4.62; N 8.65.

*4.6. 4-Phenyl-2-(trifluoromethyl)-2,3-dihydro-1*H*-pyrido[2,3-b][1,4]diazepine (3ba)*

Brown solid. Mp 125–130 °C.

^{1}H NMR (300 MHz, DMSO d^6): δ 8.02 (dd, 1H, $^3J_{HH}$ = 4.6 Hz, $^4J_{HH}$ = 1.6 Hz), 7.95–8.00 (massif, 2H), 7.63 (dd, 1H, $^3J_{HH}$ = 7.6 Hz, $^3J_{HH}$ = 1.6 Hz), 7.43–7.53 (massif, 3H), 7.17 (d, 1H, $^3J_{HH}$ = 6.4 Hz), 6.92 (dd, 1H, $^3J_{HH}$ = 7.6 Hz, $^3J_{HH}$ = 4.6 Hz), 4.83 (m large, 1H), 3.66 (dd, 1H, $^2J_{HH}$ = 15.0 Hz, $^3J_{HH}$ = 5.5 Hz), 2.86 (dd, 1H, $^2J_{HH}$ = 15.0 Hz, $^3J_{HH}$ = 1.8 Hz).

^{13}C NMR (75 MHz, DMSO d^6): δ 164.5, 151.2, 146.9, 139.9, 139.7, 131.2, 130.4, 129.3, 127.9, 126.2 (q, $^1J_{CF}$ = 283.2 Hz, CF_3), 116.4, 62.2 (q, $^2J_{CF}$ = 29.3 Hz), 29.9.

^{19}F NMR (282 MHz, $CDCl_3$): δ – 73.56 (d, $^3J_{FH}$ = 8.0 Hz).

Anal. calcd for $C_{15}H_{12}F_3N_3$: C 61.85; H 4.15; N 14.43; found: C 61.76; H 4.43; N 14.27.

*4.7. 4-(2-Naphthyl)-2-(trifluoromethyl)-2,3-dihydro-1*H*-pyrido[2,3-b][1,4]diazepine (3bb)*

Brown solid.

^{1}H NMR (300 MHz, DMSO d^6): δ 6.8–8.4 (massif, 11H), 4.90 (m large, 1H), 3.86 (dd, 1H, ^{2}JHH = 15.0 Hz), $^3J_{HH}$ = 5.5 Hz), 2.97 (dd, 1H, $^2J_{HH}$ = 15.0 Hz, ^{3}JHH = 2.1 Hz)

^{19}F NMR (282 MHz, DMSO d^6): δ – 73.42 (d, $^3J_{FH}$ = 8.0 Hz).

4.8. Trans*-4-phenyl-2-(trifluoromethyl)-2,3,5a,6,7,8,9,9a-octahydro-1*H*-1,5-benzodiazepine (3ca)*

First diastereomer (Yellow solid).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72–7.80 (massif, 2H), 7.37–7.47 (massif, 3H), 3.69 (ddq, 1H, $^3J_{HH}$ = 6.7 Hz, $^3J_{HH}$ = 8.0 Hz, $^3J_{HF}$ = 8.1 Hz), 3.15–3.46 (massif, 3H), 2.76 (m, 1H), 2.23 (m, 1H), 2.06 (bs, 1H), 1.65–1.97 (massif, 4 H), 1.25–1.56 (massif, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6, 141.2, 130.3, 128.9, 127.3, 126.5 (q, $^1J_{CF}$ = 280.9 Hz, CF_3), 66.1, 55.9, 50.7 (q, $^2J_{CF}$ = 28.9 Hz), 34.8, 32.9 (q, $^3J_{CF}$ = 1.5 Hz), 32.6, 25.8, 25.2.

^{19}F NMR (282 MHz, $CDCl_3$): δ – 76.75 (d, $^3J_{FH}$ = 8.1 Hz).

Anal. calcd for $C_{16}H_{19}F_3N_2$: C 64.85; H 6.46; N 9.45; found: C 64.53; H 6.12; N 9.62.

Second diastereomer (Yellow solid).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73–7.80 (massif, 2H), 7.36–7.47 (massif, 3H), 3.28–3.48 (massif, 3H), 2.86 (m, 1H), 2.54 (m, 1H), 2.26 (m, 1H), 2.07 (bs, 1H), 1.65–2.01 (massif, 4 H), 1.25–1.48 (massif, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 168.3, 140.7, 130.4, 128.9, 127.1, 125.8 (q, $^1J_{CF}$ = 280.3 Hz, CF_3), 66.0, 56.7 (q, $^2J_{CF}$ = 28.4 Hz), 56.5, 36.2, 35.1, 33.9 (q, $^3J_{CF}$ = 1.3 Hz), 24.91, 24.86.

^{19}F NMR (282 MHz, $CDCl_3$): δ – 78.23 (d, $^3J_{FH}$ = 6.9 Hz).

Anal. calcd for $C_{16}H_{19}F_3N_2$: C 64.85; H 6.46; N 9.45; found: C 64.95; H 6.31; N 9.83.

4.9. Trans*-4-(2-naphthyl)-2-(trifluoromethyl)-2,3,5a,6,7,8,9,9a-octahydro-1*H*-1,5-benzodiazepine (3cb)*

Yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14 (bs, 1H), 8.01 (dd, 1H, $^3J_{HH}$ = 8.7 Hz, $^4J_{HH}$ = 1.9 Hz), 7.82–7.96 (massif, 3H), 7.50–7.59 (massif, 2H), 3.60 (d, 1H, $^2J_{HH}$ = 14.3 Hz), 3.33–3.53 (massif, 2H), 2.93 (dd, 1H, $^2J_{HH}$ = 14.3 Hz, $^3J_{HH}$ = 10.4 Hz), 2.56 (m, 1H), 2.31 (m, 1H), 1.70–2.16 (massif, 5H), 1.20–1.52 (massif, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 168.0, 137.8, 134.5, 133.4, 129.3, 128.7, 128.0, 127.4, 127.0, 126.8, 125.8 (q, $^1J_{CF}$ = 280.5 Hz, CF_3), 124.6, 66.13, 56.8 (q, $^2J_{CF}$ = 28.4 Hz), 56.54, 36.2, 35.1, 33.7 (q, $^3J_{CF}$ = 1.3 Hz), 24.94, 24.88.

^{19}F NMR (282 MHz, $CDCl_3$): δ – 78.14 (d, $^3J_{FH}$ = 6.9 Hz).

Anal. calcd for $C_{20}H_{21}F_3N_2$: C 69.35; H 6.11; N 8.09; found: C 69.05; H 5.99; N 8.38.

4.10. Trans*-4-(2-furyl)-2-(trifluoromethyl)-2,3,5a,6,7,8,9,9a-octahydro-1*H*-1,5-benzodiazepine (3cc)*

Yellow solid. Mp 72–76 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (d large, 1H, $^3J_{HH}$ = 1.5 Hz), 6.82 (d, 1H, $^3J_{HH}$ = 3.5 Hz), 6.48 (dd, 1H, $^3J_{HH}$ = 3.5 Hz, $^3J_{HH}$ = 1.5 Hz), 3.20–3.44 (massif, 3H), 2.77 (dd, 1H, $^2J_{H2B-HA}$ = 14.3 Hz, $^3J_{HH}$ = 10.6 Hz), 2.53 (m, 1H), 2.25 (m, 1H), 1.64–1.98 (massif, 5H), 1.28–1.44 (massif, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 158.9, 153.0, 145.7, 125.6 (q, $^1J_{CF}$ = 280.3 Hz, CF_3), 113.1, 111.9, 66.0, 56.8 (q, $^2J_{CF}$ = 28.4 Hz), 56.7, 36.1, 35.0, 33.4 (q, $^3J_{CF}$ = 1.3 Hz), 24.9, 24.8.

^{19}F NMR (282 MHz, $CDCl_3$): δ – 78.29 (d, $^3J_{FH}$ = 6.9 Hz).

Anal. calcd for $C_{14}H_{17}F_3N_2O$: C 58.73; H 5.99; N 9.78; found: C 58.48; H 5.74; N 9.57.

4.11. 4-Phenyl-2-(trifluoromethyl)-2,3-dihydro-1,5-benzothiazepine (5aa)

White solid. Mp 94–96 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08 (m, 2H), 7.66 (dd, 1H, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.4 Hz), 7.47–7.61 (massif, 4H), 7.30 (dd, 1H, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.4 Hz), 7.16 (ddd, 1H, $^3J_{HH}$ = $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.4 Hz), 4.19 (ddq, 1H, $^3J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 5.1 Hz, $^4J_{HF}$ = 7.9 Hz), 3.41 (dd, 1H, $^3J_{HH}$ = 5.1 Hz, $^2J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 5.1 Hz), 2.87 (t, 1H, $^3J_{HH}$ = $^2J_{HH}$ = 12.9 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 167.7, 152.6, 137.4, 135.8, 132.0, 131.1, 129.4, 127.7, 126.0, 125.9 (q, $^1J_{CF}$ = 279.8 Hz, CF_3), 125.6, 120.4, 57.0 (q, $^2J_{CF}$ = 29.5 Hz), 29.1 (q, $^3J_{CF}$ = 2.0 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ – 74.09 (d, $^3J_{FH}$ = 7.9 Hz).

Anal. calcd for $C_{16}H_{12}F_3NS$: C 62.53; H 3.94; N 4.56; S 10.43; found: C 62.24; H 4.28; N 4.36; S 10.7.

4.12. 4-(2-Naphthyl)-2-(trifluoromethyl)-2,3-dihydro-1,5-benzothiazepine (5ab)

Yellow solid. Mp 134–135 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.30–8.42 (massif, 1H), 7.90–8.04 (massif, 3H), 7.50–7.72 (massif, 4H), 7.36 (dd, 1H, ^3J = 7.9 Hz, ^4J = 1.1 Hz), 7.18 (dd, 1H, ^3J = 7.6 Hz, ^4J = 1.3 Hz), 4.27 (ddq, 1H, $^3J_{HH}$ = 5.0 Hz, $^3J_{HH}$ = 13.0 Hz, $^3J_{HF}$ = 7.1 Hz), 3.57 (dd, 1H, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 5.0 Hz), 2.95 (t, 1H, $^2J_{HH}$ = $^3J_{HH}$ = 13.0 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 167.5, 152.7, 135.8, 135.3, 134.8, 133.4, 131.1, 129.5, 129.2, 128.3, 128.2, 127.2, 126.1, 125.9 (q, $^1J_{CF}$ = 279.7 Hz, CF_3), 125.6, 124.4, 120.4, 57.0 (q, $^2J_{CF}$ = 29.5 Hz), 29.0 (q, $^3J_{CF}$ = 1.8 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ – 74.08 (d, $^3J_{FH}$ = 7.1 Hz).

Anal. calcd for $C_{20}H_{14}F_3NS$: C 67.21; H 3.95; N 3.92; S 8.97; found: C 67.09; H 4.21; N 4.03; S 8.66.

4.13. 4-(2-Furyl)-2-(trifluoromethyl)-2,3-dihydro-1,5-benzothiazepine (5ac)

Brown solid. Mp 80–81 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60–7.67 (massif, 2H), 7.46 (td, 1H, $^3J_{HH}$ = $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.3 Hz), 7.28 (dd, 1H, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.3 Hz), 7.08–7.15 (massif, 2H), 6.59 (dd, 1H, $^3J_{HH}$ = 1.9 Hz, $^3J_{HH}$ = 3.4 Hz), 4.19 (ddq, 1H, $^3J_{HH}$ = 13.0 Hz, $^3J_{HF}$ = 7.3 Hz, $^3J_{HH}$ = 5.3 Hz), 3.28 (dd, 1H, $^2J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 5.3 Hz), 2.75 (dd, 1H, $^2J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 13.0 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 158.4, 152.3, 152.0, 146.4, 135.9, 131.1, 126.1, 125.9, 125.8 (q, $^1J_{CF}$ = 279.7 Hz, CF_3), 120.8, 114.6, 113.0, 56.9 (q, $^2J_{CF}$ = 29.6 Hz), 29.1 (q, $^3J_{CF}$ = 2.2 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ – 74.23 (d, $^3J_{FH}$ = 7.3 Hz).

Anal. calcd for $C_{14}H_{10}F_3NOS$: C 56.56; H 3.39; N 4.71; S 10.79; found: C 56.71; H 3.48; N 4.4; S 10.48.

4.14. 4-(1-Benzofuran-2-yl)-2-(trifluoromethyl)-2,3-dihydro-1,5-benzothiazepine (5ad)

Yellow solid. Mp 126–128 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62–7.75 (massif, 3H), 7.27–7.55 (massif, 5H), 7.16 (td, 1H, ^3J = 7.5 Hz, ^4J = 1.1 Hz), 4.26 (ddq, 1H, $^3J_{HH}$ = 5.3 Hz, $^3J_{HH}$ = 12.8 Hz, $^3J_{HF}$ = 7.8 Hz), 3.39 (dd, 1H, $^2J_{HH}$ = 12.8 Hz, $^3J_{HH}$ = 5.3 Hz), 2.85 (t, 1H, $^2J_{HH}$ = $^3J_{HH}$ = 12.8 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 156.5, 153.2, 151.9, 136.0, 131.2, 128.3, 127.7, 126.5, 126.1, 125.8 (q, $^1J_{CF}$ = 279.8 Hz, CF_3), 124.2, 122.8, 120.8, 112.6, 111.0, 57.1 (q, $^2J_{CF}$ = 29.6 Hz), 29.4 (q, $^3J_{CF}$ = 2.2 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ – 74.17 (d, $^3J_{FH}$ = 7.8 Hz).

Anal. calcd for $C_{18}H_{12}F_3NOS$: C 62.24; H 3.48; N 4.03; S 9.23; found: C 61.94; H 3.77; N 3.86; S 8.89.

4.15. 7-(Trifluoromethyl)-5,6,6a,7-tetrahydrobenzo[b]naphtho[1,2-e][1,4]thiazepine (5ae)

Green solid. Mp 95–98 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.51 (dd, 1H, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 1.3 Hz), 7.68 (dd, 1H, ^3J = 7.7 Hz, ^4J = 1.3 Hz), 7.44–7.55 (massif, 2H), 7.35–7.43 (massif, 2H), 7.29 (m, 1H), 7.12–7.21 (massif, 1H), 4.05 (dt, 1H, $^3J_{HH}$ = 12.2 Hz, $^3J_{HF}$ = 7.9 Hz), 3.32 (dt, 1H, $^3J_{HH}$ = 12.2 Hz, $^3J_{HH7}$ = 3.3 Hz), 3.08 (ddd, 1H, $^2J_{HH}$ = 17.4 Hz, $^3J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 4.2 Hz), 2.91 (ddd, 1H, $^2J_{HH}$ = 17.4 Hz, $^3J_{HH}$ = 4.0 Hz, $^3J_{HH}$ = 3.1 Hz), 2.22 (m, 1H), 2.06 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 167.7, 152.6, 140.4, 135.9, 132.0, 131.9, 131.2, 129.4, 127.9, 127.4, 126.1 (q, $^1J_{CF}$ = 280.8 Hz, CF_3), 125.6, 125.4, 120.8, 56.5 (q, $^2J_{CF}$ = 27.5 Hz), 37.9, 25.3, 25.0 (q, $^4J_{CF}$ = 2.2 Hz, C-17).

^{19}F NMR (282 MHz, $CDCl_3$): δ – 68.30 (d, $^3J_{FH}$ = 7.9 Hz).

Anal. calcd for $C_{18}H_{14}F_3NS$: C 64.85; H 4.23; N 4.2; S 9.62; found: C 64.64; H 4.59; N 4.58; S 9.68.

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