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Synthesis of trifluoromethylated [1,4]diazepines from 1,1,1-trifluoroalk-3-yn-2-ones

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Reaction of 1,1,1-trifluoroalk-3-yn-2-ones with 1,2-diamines affords trifluoromethylated [1,4]diazepines.

Diazepine derivatives exhibit anti-inflammatory, anticonvulsant, sedative and analgesic activities and can treat cancer, cardiovascular disorder and AIDS.[1] Some of them are used as dyes and ferroelectrics.[2]

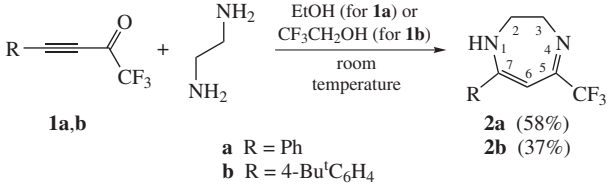
Meanwhile, incorporation of fluorine into molecule provides binding with target receptors, better membrane permeability, and blocking effect to metabolic decomposition. Nearly 25 per cent of new synthetic drugs and agrochemicals contain at least one fluorine atom or trifluoromethyl group.[3] The most promising approach to such type of compounds is the use of CF_3-bearing reactants as starting materials.

Condensation of 1,3-diketones with 1,2-diamines is a common access to non-fluorinated diazepines.[4] However, CF_3-diketones react in a different way affording benzimidazoles, amino enones, or macrocycles.[5] Considering these facts we set out a goal to obtain trifluoromethylated diazepines from CF_3-containing α,β-ynones. Recently we have found unusual rearrangement with 1,2-shift of CF_3 group in the reaction of CF_3-bearing α-bromo enones with diamines.[6]

Acetylenic ketones are used for the synthesis of diazepines in reactions with binucleophiles.[7] However, this approach to target heterocycles from CF_3-ynones is still scarce. High polarity of acetylenic bond and different nature of electrophilic *sp*- and sp^2-centers in ynones can provide higher selectivity of such reactions. Herein we report results of investigation of 1,1,1-trifluoroalk-3-yn-2-ones **1a**–**d** with 1,2-diamines.

Unsubstituted ethylenediamine reacts with ynones **1a**,**b** giving target diazepines **2a**,**b** in moderate yield (Scheme 1).† Their enamine tautomeric form seems to be more preferable due to the longer conjugation chain.

Mono-substituted analogue of ethylenediamine reacts with CF_3-ynones less selectively. Thus, the treatment of ynone **1a** with *N*-methylethylenediamine under the optimal reaction conditions led to the mixture of target heterocycle **3** and acyclic products of mono- and bis-addition **4a** and **5** in moderate yield.‡ Ynone **1c** in this reaction transforms exclusively into amino enone **4b** (Scheme 2). *E*,*Z*-Configuration of bis-adduct **5** was proved by 2D NMR spectroscopy (NOESY and HMBC) data. We did not find any influence of the solvent on the reaction course: the similar results were obtained in both protic (ethanol) and aprotic (benzene) media. These results indicate that the attack



1a,**b**

a R = Ph
b R = 4-Bu^{t}C$_6$H$_4$

2a (58%)
2b (37%)

Scheme 1

† *General procedure*. A mixture of appropriate ynone (**1a**,**c**,**d**) (1.0 mmol) and *o*-phenylenediamine (1.0 mmol) (in the case of **7a**–**c**) or ethylenediamine (**2a**,**b**) in ethanol or benzene (2 ml) was stirred at room temperature for 24 h. The volatiles were evaporated *in vacuo*, the residue was purified by column chromatography [silica gel, diethyl ether–hexane (1:3) or $CHCl_3$–MeOH (95:5)]. Heterocycles **2a**,**b**, **7a**–**c** were obtained by this method. Products **7c** and **8** were described earlier.[9]

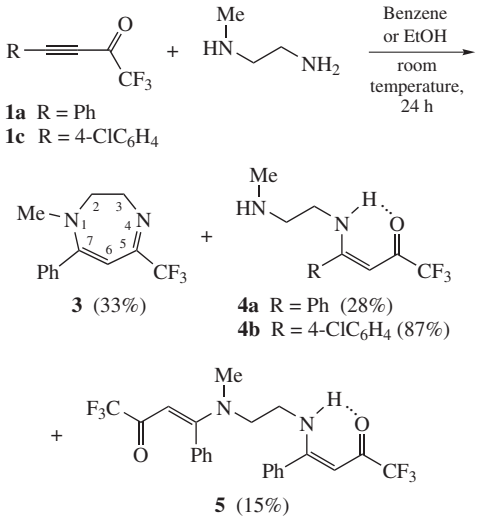
*7-Phenyl-5-trifluoromethyl-2,3-dihydro-1*H*-[1,4]diazepine* **2a**. Brownish viscous oil, yield 139 mg (58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.53 (s, 2H, C^2H_2), 4.00 (s, 2H, C^3H_2), 4.96 (br. s, 1H, NH), 5.33 (s, 1H, C^6H), 7.40–7.65 (m, 5H, Ph). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 48.7, 56.0 (C^2, C^3), 87.5 (C^6), 121.3 (q, CF_3, *J* 279.8 Hz), 127.4, 129.0, 130.7, 138.0 (Ph), 156.6 (q, C^5, *J* 31.0 Hz), 158.7 (C^7). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ: –71.3. MS (EI), *m*/*z* (%): 240 (100, M^+), 212 (33), 192 (26), 172 (26), 143 (50), 115(31). HRMS (ESI), *m*/*z*: 263.0774 (calc. for $C_{12}H_{11}F_3N_2Na^+$ [M + Na^+], *m*/*z*: 263.0767).

For characteristics of 7-(4-*tert*-butylphenyl)-5-trifluoromethyl-2,3-dihydro-1*H*-[1,4]diazepine **2b**, see Online Supplementary Materials.

‡ *1-Methyl-7-phenyl-5-trifluoromethyl-2,3-dihydro-1*H*-[1,4]diazepine* **3**. Light yellow oil, yield 85 mg (33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.75 (s, 3H, Me), 3.20 (br. s, 2H, C^3H_2), 3.98 (br. s, 2H, C^2H_2), 5.22 (s, 1H, C^6H), 7.30–7.45 (m, 5H, Ph). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 43.8 (NMe), 55.5, 56.2 (C^2, C^3), 92.1 (C^6), 121.5 (q, CF_3, *J* 279.1 Hz), 128.6, 128.9, 129.9, 138.5 (Ph), 155.6 (q, C^5, *J* 30.3 Hz), 161.1 (C^7). Found (%): C, 61.27; H, 4.85; N, 10.44. Calc. for $C_{13}H_{13}F_3N_2$ (%): C, 61.41; H, 5.15; N, 11.02.

1,1,1,12,12,12-Hexafluoro-5-methyl-4,9-diphenyl-5,8-diazadodeca-3,9-diene-2,11-dione **5**. White solid, yield 34 mg (15%). IR (KBr, ν/cm^{-1}): 1175, 1188 (C–F), 1524, 1615, 1656 (C=O, C=C, Ph). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.88 (s, 3H, NMe), 3.36 (br. s, 4H, C^6H_2, C^7H_2), 5.28, 5.46 (2s, 2H, C^3H, $C^{10}H$), 6.65–7.60 (m, 10H, 2Ph), 10.97 (br. s, 1H, NH). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ: –76.7. ^{15}N NMR (40.6 MHz, $CDCl_3$) δ: –267.1. MS (EI), *m*/*z* (%): 471 (M^+ + 1, 1), 253 (54), 242 (34), 184 (100), 146 (40). Found (%): C, 59.03; H, 4.12; N, 5.97. Calc. for $C_{23}H_{20}F_6N_2O_2$ (%): C, 58.73; H, 4.29; N, 5.95.

For characteristics of compounds **4a**,**b**, see Online Supplementary Materials.

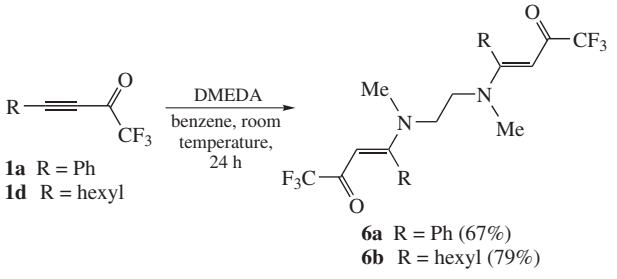


Scheme 2

onto the triple bond of ynones **1a**,**c** occurs with the participation of both primary and secondary amino groups of diamine. When attacking nucleophile center is secondary amino group, the forming intermediate undergoes intramolecular cyclization giving [1,4]diazepine **3** or reacts with another molecule of ynone producing bis-adduct **5**.

Amino enone **4a** seems to be the precursor of the bis-adduct **5**. As we expected, reaction of ynones **1a**,**d** with symmetrically disubstituted *N*,*N*′-dimethylethylenediamine (DMEDA), performed under the same experimental conditions, exclusively afforded bis-adducts **6a**,**b** (Scheme 3). ^{1}H NMR and NOESY experiments, performed in $CDCl_3$ solution at room temperature, demonstrated the presence of a single *E*,*E*-isomer (see Online Supplementary Materials). The results obtained allow us to resume that secondary amino group is not susceptible to intramolecular cyclization and aza-Michael adduct as intermediate undergoes next the addition of the second molecule of ynone to yield the final reaction product **6**. Recently it was reported that this kind of compounds was used as ligands with transition metal ions to form metallomesogens.[8]

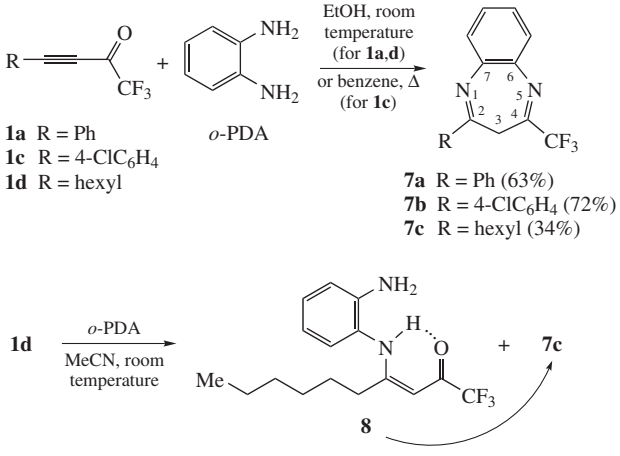
o-Phenylenediamine (*o*-PDA) reacts in the same manner as ethylenediamine affording benzodiazepines **7a–c** in good yields (Scheme 4).[§] The moderate yield in the case of ynone **1d** is



Scheme 3

[§] *2-Phenyl-4-trifluoromethyl-3*H-*benzo*[b]*[1,4]diazepine* **7a**. Light yellow solid, yield 182 mg (63%), mp 75–76 °C. IR (KBr, ν/cm^{-1}): 1170, 1183, 1194 (C–F), 1590 (Ar), 1611 (Ph), 1640 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.47 (br. s, 2 H, C^3H_2), 7.3–8.08 (m, 9 H, Ar). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 32.2 (C^3), 121.9 (q, CF_3, J 266.0 Hz), 126.1, 127.9, 128.8, 129.0, 131.5, 136.2, 137.3 (Ar), 144.7 (q, C^4, J 35.5 Hz), 153.7 (C^2). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ: –70.9. ^{15}N NMR (40.6 MHz, $CDCl_3$) δ: –69.2, –54.6. MS (EI), *m*/*z* (%): 288 (100, M^+), 219 (78), 89 (10). Found (%): C, 66.20; H, 4.14; N, 9.57. Calc. for $C_{16}H_{11}F_3N_2$ (%): C, 66.67; H, 3.85; N 9.72.

For characteristics of compounds **7b**,**c**, see Online Supplementary Materials.

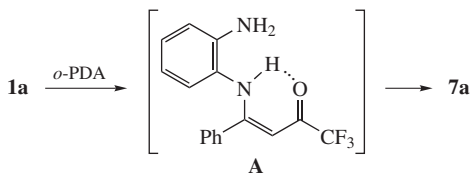


Scheme 4

explained by the simultaneous formation of mono and bis-aza-Michael adducts. We showed that ketone **8** is precursor of diazepine **7c**. Thus, NMR spectrum of amino enone **8**, isolated by column chromatography on silica gel, contained the signals of forming cyclic product **7c** and their intensity was gradually increasing.[9]

In order to get more knowledge on the mechanism of the ring formation, we performed NMR monitoring of the reaction of ynone **1a** with *o*-PDA. 1D, 2D and dynamic NMR spectra analysis allowed us to detect the principal intermediates and to follow their further transformations in the course of reaction.

Thus, the ^{19}F NMR spectrum recorded immediately after the reaction start contains the signals of the initial ketone **1a** (δ –77.8 ppm) and two intermediates (δ –76.5 and –83.6 ppm) in a ratio of 1:0.1:0.1. After standing at room temperature for 5 min, the second intermediate (δ –83.6 ppm) disappears and the ratio ketone : intermediate is 1:0.4 which changes to 1:1.25 within 30 min. After consumption of the starting ketone this intermediate becomes a principal component. Its ^{1}H NMR spectrum exhibits singlet of an olefinic proton (δ 5.80 ppm). In the ^{13}C NMR spectrum, the quartets of carbonyl (δ 177.5 ppm, J 33.0 Hz) and trifluoromethyl (δ 117.6 ppm, J 288.0 Hz) groups as well as singlets of sp^2-carbon atoms (δ 92.3 and 169.1 ppm) are observed. These spectral data confirm clearly the structure of a push-pull amino enone **A**. Its *Z*-configuration was proved with ^{1}H-^{1}H 2D NOESY NMR: there is an intensive cross-peak between an olefinic proton and *ortho*-protons of a phenyl group. The formation of the only one geometric isomer can be explained by the presence of an intramolecular hydrogen bond in its structure providing higher stability. After keeping for several hours at room temperature, the signal of intermediate **A** gradually disappears and at the same time the signal of a product **7a** (δ –70.9 ppm) grows.



Scheme 5

In summary, we have suggested a procedure for the synthesis of trifluoromethyl-containing [1,4]diazepines, which excels earlier reported method based on 1,3-diketones. The target heterocycles are formed under mild conditions in good yields and with high selectivity. The ring closure occurs *via* formation of aza-Michael adduct as a principal intermediate.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2014.09.007.

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