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A New Route to 5-Trifluoromethyl-2,3-dihydro-1,4-diazepine and 2-Trifluoromethylbenzimidazole

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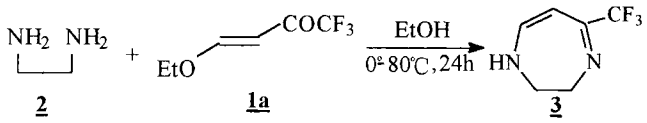
ABSTRACT: *Ethylenediamine reacted readily with 4-ethoxy-1,1,1-trifluoro-3-butene-2-one to form 5-trifliuoromethyl-2,3-dihydro-1,4-diazepine in good yield. Under the same reaction conditions, o-phenylenediamine gave 2-trifluoromethylbenzimidazole and benzimidazole.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:27–30, 2000

INTRODUCTION

It is well known that regioselective replacement of hydrogen in an aromatic or heterocyclic system by a fluorine atom or a fluoroalkyl group may have a profound influence on the biological and physical properties of such molecules [1,2]. As a result, in recent years, considerable efforts have been devoted to the development of methodologies for the preparation of fluorine-containing compounds [3–7]. α,β-Unsaturated ketones substituted with a trifluoromethyl group represent interesting building blocks for such syntheses. For example, 4-ethoxy-1,1,1-trifluoromethyl-3-butene-2-one has been widely used to prepare many trifluoromethyl or trifluoroacetyl substituted heteroaromatic compounds [8–9]. Recently, we prepared 5-trifluoromethyl-2,3-dihydro-1,4-diazepine and 2-trifluoromethylbenzimidazole by the reaction of $EtOCH=CHCOCF_3$ with ethylenediamine and *o*-phenylenediamine, respectively. Herein we wish to report these results in detail.

RESULTS AND DISCUSSION

It is well known that nitrogen nucleophiles such as amines, aniline, and hydrazine react readily with fluorine-containing α,β-unsaturated carbonyl compounds. In our previous work, we reported the reaction of 4-ethoxy-1,1,1-trifluoromethyl-3-butene-2-one **1a** with many nitrogen nucleophiles [10]. We continued this work and studied the reactions of **1a** with dinucleophiles. It was found that, under mild reaction conditions, ethylenediamine reacted smoothly with **1a** to give 5-trifluoromethyl-2,3-dihydro-1,4-diazepine in good yield.



2 **1a** **3**

In this reaction, the two amino groups attacked the double bond carbon atom and the carbonyl carbon atom, respectively, with subsequent elimination of water to afford the product **3.** It is a yellowish solid and easy to crystallize from many organic solvents, such as ethanol (EtOH), ether, and CH_3CN. The chemical shifts of the 6,7-double-bond hydrogen at-

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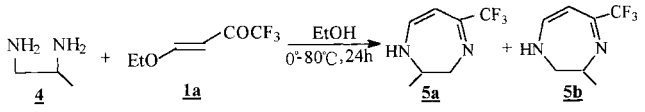
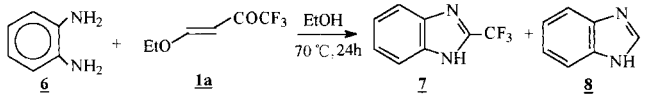
oms are observed at 6.78 ppm and 4.92 ppm, with a coupling constant of 9Hz. Its IR spectral data are identical with those reported by Wang et al. [11].

1,2-Diaminopropane reacted with **1a** in the same way and, as expected, gave two isomeric products (**5a** and **5b**) in a nearly 1:1 ratio. They can be separated cleanly by column chromatography.



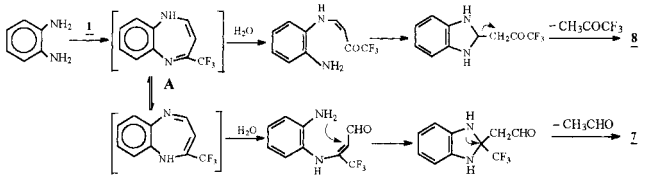
When other diamines, such as 1,3-diaminopropane and 1,4-diaminobutane were used instead of ethylenediamine, none produced the corresponding ring products.

o-Phenylenediamine, whose structure should favor 1,2-addition [3], reacted smoothly with **1a**. However, it did not give the corresponding 2,3-diazepine derivative. Instead, the products were 2-trifluoromethylbenzimidazole **7** (74%) and benzimidazole **8** (5%):

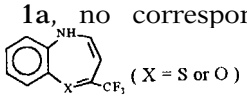


Molecule **7** is a known compound. It was first synthesized from the reaction of *o*-phenylenediamine with trifluoroacetonitrile, but the literature reference only reported the IR spectra and elemental analysis data [12]. The molecular structure of compound **7** is shown in Figure 1.

In this reaction, the 2,3-diazepine derivative **A** may be first formed as an intermediate. A possible reaction pathway for the formation of products **7** and **8** is suggested as follows:



It was interesting to find that *o*-phenylenediamine reacted similarly with 5-trifluoroacetyl-2,3-dihydrofuran **1b** or 5-trifluoroacetyl-2,3-dihydropyran **1c** to give two products **7** and **8**, but the main product was **8**.

However, under the same reaction conditions, when other dinucleophiles, such as 2-aminothiophenol **9a** reacted with **1a**, no corresponding heterocyclic products  were

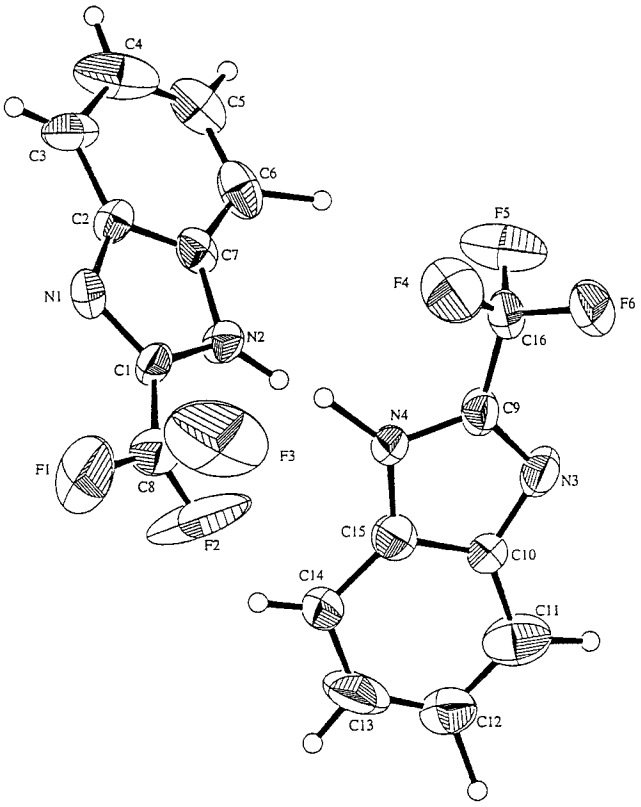
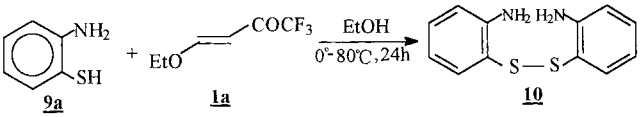
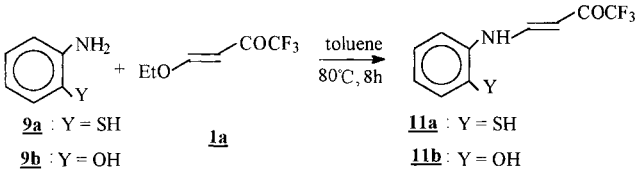


FIGURE 1 The molecular structure of compound **7**.

formed. The reaction product was 2,2′-dithiobisbenzenamine **10**, whose spectral data matched those found in the literature report [13].



When the reaction was carried out in toluene, the dinucleophiles 2-aminothiophenol **9a** or 2-aminophenol **9b** reacted easily with **1a** to give **11a** or **11b** in good yield:



Compounds **11a** and **11b** are thermally stable when heated in toluene at 110°C for 2 hours. All the reaction results of **1** with dinucleophiles are summarized in Table 1.

TABLE 1 Reaction results of **1** with Dinucleophiles

			Condition[a]				
Entry	*Substrate*	*Reagent*	*Solution*	*t/(°C)*	*T/(h)*	*Products*	*Yields (%)*
1	**1a**	**2**	C_2H_5OH	0–80	24	**3**	92
2	**1a**	**4**	C_2H_5OH	0–80	24	**5a**	34
						5b	34
3	**1a**	**6**	C_2H_5OH	70	24	**7**	72
						8	5
4	**1b**	**6**	C_2H_5OH	70	24	**7**	15
						8	60
5	**1c**	**6**	C_2H_5OH	70	24	**7**	25
						8	45
6	**1a**	**9a**	C_2H_5OH	70	24	**10**	85
7	**1b**	**9a**	C_2H_5OH	r.t.	24	**10**	85
8	**1c**	**9a**	C_2H_5OH	r.t.	24	**10**	87
9	**1a**	**9a**	C_6H_5-CH_3	80	8	**11a**	88
10	**1a**	**9b**	C_6H_5-CH_3	80	24	**11b**	94

[1]r.t., room temperature.

EXPERIMENTAL

The melting points were measured on a Temp-Melt. apparatus and are uncorrected. Solvents were purified and dried before use. ^{1}HNMR (60 MHz) and ^{19}F NMR (54.6 MHz) spectra were recorded on a Varian-360L instrument or Bruker AM-300 spectrometer with tetrameythlsilane (TMS) and trifluoroacetyl (TFA) ($\delta_{CFCl3} = \delta_{TFA} + 76.8$ ppm.) as the internal and external standards. IR spectra were obtained with an IR-440 Shimadzu spectrophotometer. Lower resolution mass spectra and high resolution mass spectra (HRMS) were obtained on a Finnigan GC-MS 4021 and Finnigan MAT-8430 instrument, respectively. X-ray structure analysis was performed with a Rigaku/AFC 7R Diffractometer. Elemental analyses were performed by this Institute. Compound **1a** was prepared according to a method in the literature [2].

Reaction of **1** *with Ethylenediamine*

Ethylenediamine (0.6 g, 10 mmol) was added into a 25 mL flask containing a solution of **1a** (1.68 g, 10 mmol) and EtOH (10 mL). This reaction mixture was stirred for 4 hours at room temperature and continually stirred for 20 hours at 80°C. The reaction process was monitored by thin-layer chromatography (TLC). The crude product solidified from the solvent. Recrystallization of the crude product from ether gave the pure product **3a** (1.5 g, 92%). Its spectral data are identical with the literature report [11].

Similarly, treatment of **1a** with 1,2-diaminopropane gave **5a** and **5b**. The two isomers can be separated by column chromatography.

2-Methyl-5-trifluoromethyl-2,3-dihydro-1,4-diazepine **5a**. m.p. 183–185°C (HRMS for $C_7H_9F_3N_2$ Calcd, 178.0718; Found, 178.0719); ν_{max}(KBr)/cm^{-1}: 3213(m, N-H), 2986(m, C-H), 1632(m, C=C), 1560(s, C=N), 1189, 1125(vs, C-F); δ_H:(90MHz, CCl_4) 6.58(d, J = 9Hz, 1H), 4.87(d, J = 9Hz, 1H), 3.48, (m, 1H), 3.55(m, 2H), 1.13(d, 3H), 6.90(br, NH); δ_F:(60 MHz CCl_4) −71.1(s, CF_3); *m/z%*: 179(M^+ + H, 26.85), 178(M^+, 92.22), 163(M^+-CH_3, 13.41), 149(M^+-C_2H_5, 31.69), 136(M^+-C_3H_6, 100.00) 109(M^+-CF_3, 12.41).

3-Methyl-5-trifluoromethyl-2,3-dihydro-1,4-diazepine **5b**. m.p. 184–186°C (HRMS for $C_7H_9F_3N_2$ Calcd, 178.0718; Found, 178.0719); ν_{max}(KBr)/cm^{-1}: 3213(m, N-H), 2986(m, C-H), 1632(m, C=C), 1560(s, C=N), 1189, 1125(vs, C-F); δ_H:(90MHz, CCl_4) 6.56(d, J = 9Hz, 1H), 4.77(d, J = 9Hz, 1H), 3.78, (m, 1H), 3.07(m, 2H), 1.20(d, 3H), 6.80(br, NH); δ_F:(60 MHz CCl_4) −71.2(s, CF_3); *m/z%*:179(M^+ + H, 26.85), 178(M^+, 92.22), 163(M^+-CH_3, 13.41), 149(M^+-C_2H_5, 31.69), 136(M^+-C_3H^6, 100.00) 109(M^+-CF_3, 12.41)

Reaction of **1** *with o-Phenylenediamine*

o-Phenylenediamine (1.1 g, 10 mmol) was added into a 25 mL flask containing a solution of **1a** (1.7 g, 10 mmol) and EtOH (10mL). This reaction mixture was stirred at room temperature and continually stirred for 20 hours at 80°C. After the reaction mixture was stirred for about 24 hours the TLC analysis showed that the reaction was finished. The solvent was evaporated. The crude product was sublimated in a vacuum and then separated by column chro-

matography to give the pure products **7** (1.33 g, 72%) and **8** (0.6 g, 5%).

2-Trifluoromethylbenzimidazole **7**. m.p. 209–210°C δ_H:(90 MHz, CD_3COCD_3) 7.50(m, 2H), 7.19(m, 2H), 3.20(br, NH); δ_F:(60 MHz CD_3COCD_3) −64.0(s, CF_3); *m/z%*:187(M^+ + H, 11.66), 178(M^+, 100.00), 116(M^+-CF_3-H, 18.29), 90(C_6H_4 + N, 17.06).

Reaction of **1** *with 2-Aminothiophenol*

At room temperature, 2-aminothiophenol **9a** (1.25 g, 10 mmol) was added to a 25 mL flask containing a solution of **1a** (1.68 g, 10 mmol) and toluene (10 mL). After the mixture was stirred for about 8 hours the solvent was evaporated. The crude product was purified by column chromatography to give the pure yellowish product **11a** (2.17g, 88%). However, treatment of **9a** with **1a**, **1b**, and **1c** in EtOH gave the same product **10**.

4-(2-Mercaptophenyl)amino-1,1,1-trifluoromethyl-3-butene-2-one **11a**. m.p. 168–171°C (HRMS for $C_{10}H_8F_3NOS$ Calcd, 247.0279; Found, 247.0263); ν_{max}(KBr)/cm^{-1}: 3446(w, N-H, S-H), 1645(m, C=O), 1600(m, C=C), 1564(s, C=N), 1140, 1073(vs, C-F); δ_H:(90 MHz, $CDCl_3$) δ7.40(m, 1H), 7.20(d, 4H), 7.01(br, NH), 5.49(d, 1H); δ_F:(60 MHz $CDCl_3$) δ − 75.3 (s, CF_3); *m/z(%)*: 247(M^+, 56.95), 246(M^+-H, 61.48), 176(M^+-CF_3-H, 43.28), 149(M^+-$COCF_3$, 100.00), 109(C_6H_4SH, 18.36).

Reaction of **1** *with 2-Aminophenol*

At room temperature, 2-aminophenol **9b** (1.1 g, 10 mmol) was added to a 25 mL flask containing a solution of **1a** (1.7 g, 10 mmol) and toluene (10 mL). This reaction mixture was stirred at 80°C for about 24 hours. The TLC showed that the reaction was nearly finished, The reaction mixture was cooled to room temperature, and the crude product was crystallized from toluene. Recrystallization from ether gave the pure product **11b** (2.18 g, 94%).

4-(2-Hydroxyphenyl)amino-1,1,1-trifluoromethyl-3-butene-2-one **11b**. m.p. 183–185°C (Anal calcd for $C_{10}H_8F_3NO_2$: N, 6.06%; H, 3.46%; C, 51.95%; Found: N, 6.15%; H, 3.27%; C, 51.67%); ν_{max}(KBr)/cm^{-1}: 3354(vs, N-H,O-H), 1633(s, C=O), 1614(s, C=C), 1569(s, C=N), 1135, 1080(s, C-F); δ_H: (90 MHz, $CDCl_3$) δ10.12(br, NH), 8.00(m, 1H), 7.36(d, 4H), 7.14(m, 4H), 5.79(d, 1H); δ_F:(60MHz D-DMSO) δ − 73.9(s, CF_3); m/z(%): 232(M^+ + H, 14.56), 231(M^+, 69.70), 162(M^+-CF_3, 100.00), 134 (M^+-$COCF_3$, 15.93), 93(C_6H_4OH, 6.29).

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