DOMINO REACTIONS WITH 5-AZIDO- AND 5-AMINO-4-TRIFLUOROMETHYL-1,3-AZOLES.

Klaus Burger*, Eva Höß, Lothar Hennig and Lothar Beyer**

RESUMEN

Reacciones dominó con 5-azido- y 5-amino-4-trifluorometil-1,3 azoles.

Los compuestos con sus sub-estructuras como CF_3-C=C-NH-R, son considerablemente reactivos frente a aminas primarias. Ellos se comportan "*ortho*-fluoruros" y son fácilmente susceptibles respecto a la eliminación / adición de restos. Éstos pueden ser enlazados uno con otro dando así reacciones tipo dominó.

Palabras clave: 5-Fluoro-4-trifluormetil-1,3-azoles; 5-azido-4-trifluormetil-1,3-azoles; 5-amino-4-trifluor-metil-1,3-azoles, reacciones tipo dominó; [1.4] eliminación HF; adición Michael.

ABSTRACT

Compounds with substructures like CF_3-C=C-NH-R are remarkable reactive towards primary amines. They behave like "*ortho*-fluorides" and are readily susceptible to elimination / addition sequences which can be linked together and performed as domino reactions.

Keywords: 5-Fluoro-4-trifluoromethyl-1,3-azoles, 5-azido-4-trifluoromethyl-1,3-azoles, 5-amino-4-trifluoromethyl-1,3-azoles, domino reaction, [1.4] HF-elimination, Michael addition

INTRODUCTION

Domino reactions offer preparatively simple and elegant solutions of complex synthetic problems.[1] The efficiency of this concept relies on linking together single reaction steps, thus avoiding separation and purification procedures after each step. When certain structural requirements are met, perfluoroalkyl substituted compounds readily undergo domino reactions.[2]

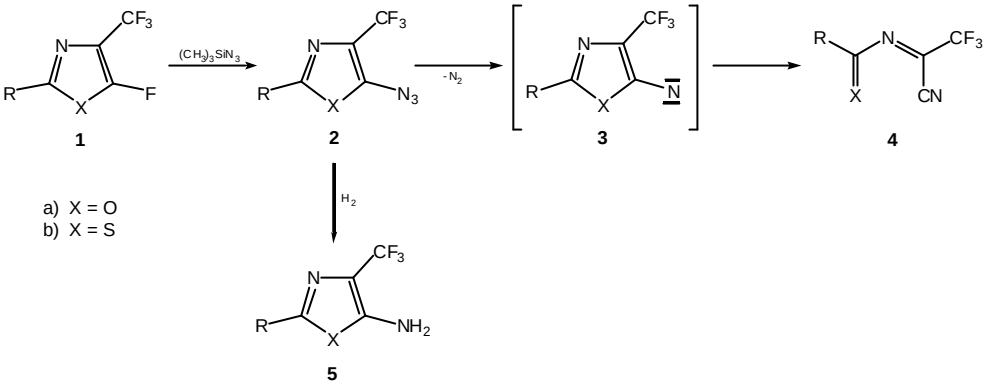
RESULTS AND DISCUSSION

Although the trifluoromethyl group is often considered to be chemically inert,[3,4] it is known to undergo a variety of reactions. The hydrolytic behavior of a trifluoromethyl group is very much dependent on its position in a molecule. Trifluoromethyl groups attached to carbon atoms possessing acidic hydrogen atoms are susceptible to hydrolysis in basic media.[5] For this reason 3,3,3-trifluoroalanine and its derivatives are unstable above pH 8.5 even at room temperature. The trifluoromethyl group undergoes hydrolysis to give a carboxylate moiety.[6] Likewise, trifluoromethyl groups attached to certain positions of heterocyclic systems undergo facile base-induced hydrolysis, e.g. 2-trifluoromethylimidazole.[7]

* Department of Organic Chemistry, University of Leipzig, Johannisallee 29, D-04103 Leipzig, Germany

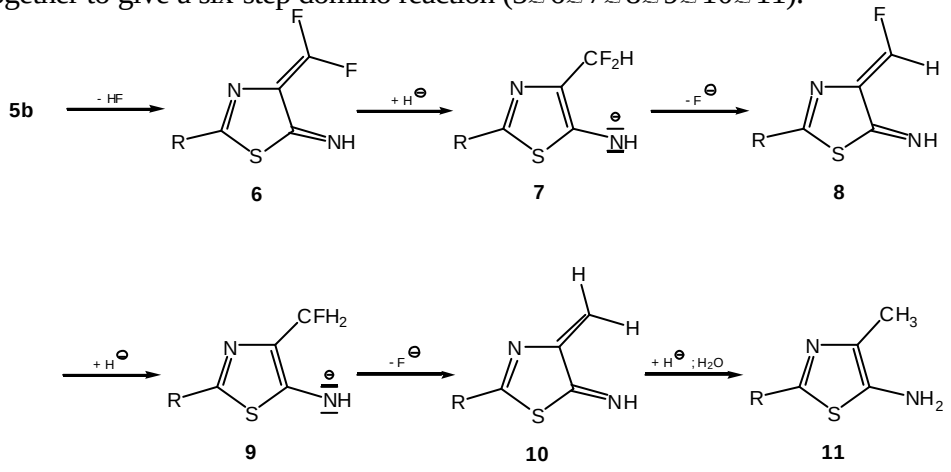
** Department of Inorganic Chemistry, University of Leipzig, Johannisallee 29, D-04103 Leipzig, Germany

5-Amino-4-trifluoromethyl-1,3-azoles (**5**)[8] are readily available from 5-fluoro-4-trifluoro-methyl-1,3-azoles (**1**)[9] *via* 5-azido-4-trifluoromethyl-1,3-azoles (**2**).[10] While compounds **2a** decompose already at room temperature within 1-2 hours to give 4-cyano-4-trifluoromethyl-1-oxa-3-aza-1,3-butadienes (**4**) with elimination of nitrogen,[11] the corresponding 5-azido-4-trifluoromethyl-1,3-thiazoles (**5**) are considerable more stable. Therefore, 5-amino-4-trifluoromethyl-1,3-oxazoles (**5a**), 5-azido- (**2b**) and 5-amino-4-trifluoromethyl-1,3-thiazoles (**5b**) represent useful model compounds to study new types of domino reactions.



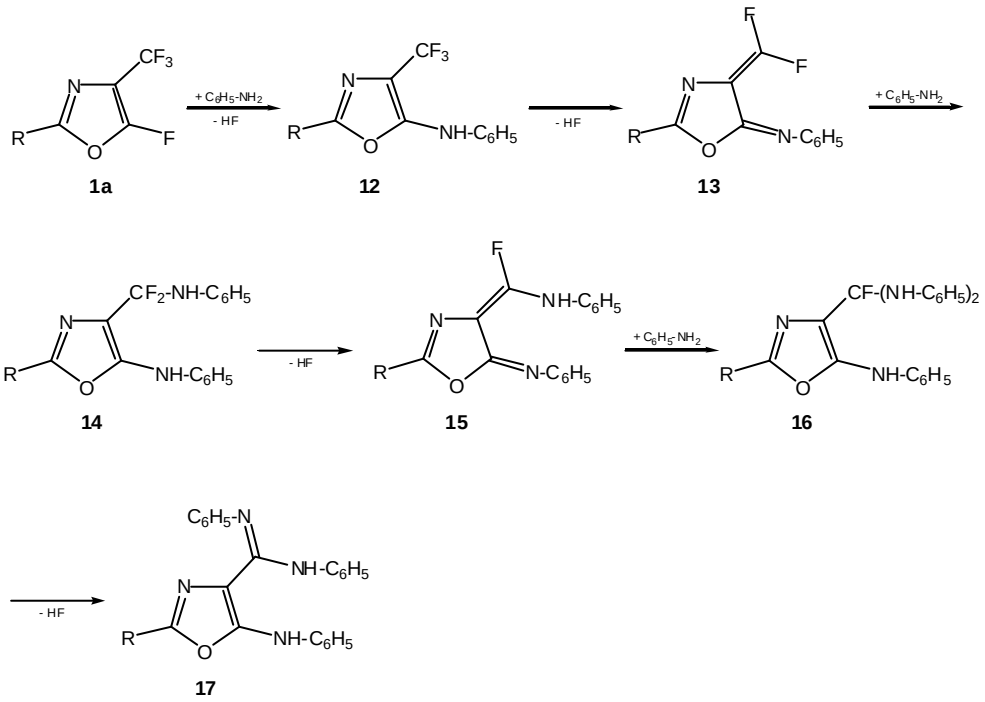
Scheme 1

Under surprisingly mild conditions a complete F/H-exchange of a trifluoromethyl group can be achieved when compounds 2b and 5b are treated with $LiAlH_4$ in diethyl ether at room temperature. Starting from 5b, three cycles, each consisting of two steps, namely [1.4]-elimination followed by addition of a hydride ion, are linked together to give a six-step domino reaction (5⇙6⇙7⇙8⇙9⇙10⇙11).



Scheme 2

This reaction sequence can be applied for a concise decoration of heterocyclic systems bearing subunits like $CF_3CH=CHNH$- with interesting substituent patterns. For example, 5-fluoro-4-trifluoromethyl-1,3-oxazole (**1a**) was heated with an excess of freshly distilled aniline (bath temperature: 40 °C) until ^{19}F NMR spectroscopy indicates complete consumption of the organic fluorine compound. Elemental analysis and mass spectrometry indicate that the compound obtained after work-up and recrystallization from chloroform/hexanes (3:1) has a molecular weight of 430.51 which is in agreement with the formula $C_{28}H_{22}N_4O$. Consequently, four equivalents of HF have been eliminated from the starting material **1a**, while three equivalents of aniline have been added during the reaction sequence.



Scheme 3

The first step of the domino reaction is a nucleophilic displacement reaction of the single fluorine bound to C-(5) (**1** ? **12**). The subunit $CF_3C=C$-NH-C_6H_5 is capable for a 1.4-HF-elimination to give a highly reactive Michael system (13), since the consecutive addition is driven by rearomatization (**13** ? **14**). The newly formed subunit H_5C_6NH-$CF_2C=C$-NH-C_6H_5 again undergoes a 1.4-HF-elimination (14 ? 15) followed by a Michael addition (**15** ? **16**). The final step of the sequence is a HF-elimination (**16** ? **17**) to form an amidine moiety. When the core unit $CF_3C=C$-NH-R is present twice in a molecule, it should be possible to run two domino reactions – with six steps each – parallel in a one-pot procedure.[12]

EXPERIMENTAL

General

Solvents were purified and dried prior to use. Reagents were used as purchased. Flash chromatography was performed using silica gel (32-63 ìm) with solvent systems given in the text. Melting points (uncorrected) were determined with a Tottoli apparatus (Fa. Büchi). ^{1}H (200 MHz, 360 MHz), ^{13}C (50 MHz, 75 MHz) and ^{19}F (188 MHz, 282 MHz) NMR spectra were recorded on Bruker WP 200, Bruker AM 360, Jeol C 60 HL and Jeol FX 90 Q spectrometers. TMS was used as reference for ^{1}H and ^{13}C NMR spectra (internal), and CF_3COOH for ^{19}F NMR spectra (external). IR spectra were obtained on Perkin Elmer 157 G and 257 spectrometers. Mass spectra were recorded on a Varian MAT CH 5 spectrometer at 70 eV.

5-Amino-4-methyl-2-(4-methylphenyl)thiazole (11)

Method A: To a suspension of $LiAlH_4$ (0.76 g, 20 mmol) in dry ether (25 mL) at -50 °C a solution of 5-azido-2-(4-methylphenyl)-4-trifluoromethylthiazole (**2b**)[10] (2.84 g, 10 mmol) in dry ether (25 mL) was added with stirring. The reaction mixture was slowly warmed up to room temperature and stirred for 16 h. Unreacted $LiAlH_4$ was destroyed on addition ice/water (20 mL). After filtration the organic phase was twice extracted with water (20 mL) and dried with $MgSO_4$. After removal of the solvent *in vacuo* the residue was purified by column chromatography (eluent: chloroform).

Method B: To a suspension of $LiAlH_4$ (0.76 g, 20 mmol) in dry ether (10 mL) a solution of 5-amino-2-(4-methylphenyl)-4-trifluoromethylthiazole (**5b**)[8] (2.58 g, 10 mmol) in dry ether (10 mL) was added at -50 °C with stirring. After stirring at -50 °C for 2 h the reaction mixture was slowly warmed up to room temperature and stirred for further 16 h. After careful treatment with ice/water (20 mL), the mixture was filtrated and the organic phase extracted twice with water (20 mL). The organic phase was dried with $MgSO_4$, evaporated to dryness and the residue purified by column chromatography (eluent: chloroform).

Yield: 0.62 g, 30% (method A); 0.80 g 39% (method B); mp 113 °C; IR (KBr). ? = 3440, 3260, 3170, 2940, 1620, 1565, 1535, 1465 cm^{-1}; ^{1}H NMR (acetone-d_6): ? = 2.32 (s, 3H), 2.38 (s, 3H), 7.25 (m, 2H), 7.82 (m, 2H); ^{13}C NMR (acetone-d_6): ? = 14.9, 21.3, 126.4, 130.4, 132.4, 140.3, 140.5, 144.7, 161.5; MS (70 eV) m/z = 204 $[M]^+$, 171 $[M - HS]^+$, 135 $[C_8H_7S]^+$, 118 $[C_8H_8N]^+$; anal. cald for $C_{11}H_{12}N_2S$ (204.27): C 64.68, H 5.92, N 13.71; found: C 64.47, H 5.40, N 13.80.

5-[(N-Phenylamino)-2-phenyloxazol-4-yl]-N,N´-diphenyl-formamidine (**17**): 5-Fluoro-4-trifluoromethyl-1,3-oxazole (**1a**)[9] (1.15 g, 5 mmol) was added to freshly distilled aniline (15 mL), then the stirred mixture was heated (bath temperature: 40 °C) for ca. 6 d. The progress of the reaction was monitored by ^{19}F NMR spectroscopy. When the conversion of the starting material was complete, the reaction mixture was partitioned between chloroform (25 mL) and water (25

mL). The organic phase was separated and twice treated with water (25 mL), dried with $MgSO_4$ and evaporated to dryness *in vacuo*. The remaining residue was recrystallized from chloroform/hexanes (3:1).

Yiel d: 1.05 g (49%); mp 154 – 156 °C; IR (KBr): ? = 1700, 1590, 1490, 1430 cm^{-1}; ^1H NMR ($CDCl_3$): ? = 6.80 – 7.43 (m, 20H), 8.30 (s, br., 1H), 10.45 (s, 1H); ^{13}C NMR ($CDCl_3$): ? = 107.2, 121.6, 122.0, 124.2, 124.4, 127.4, 127.6, 127.9, 128.2, 128.4, 128.5, 129.1, 130.5, 135.6, 137.3, 137.5, 142.6, 149.9, 165.4; MS (70 eV) m/z = 430 $[M]^+$, 337 $[M - C_6H_5NH_2]^+$, 105 $[C_6H_5CO]^+$, 93 $[C_6H_5NH_2]^+$, 77 $[C_6H_5]^+$; anal. calcd for $C_{28}H_{22}N_4O$ (430.51): C 78.11, H 5.15, N 13.00; found: C 77.64, H 5.75, N 13.41.

ACKNOWLEDGEMENTS

We thank Deutsche Forschungsgemeinschaft and Fonds der Chemischen Industrie for financial support.

Dedicated: A la «Revista de la Sociedad Química del Perú» por los 70 años de su publicación trimestral ininterrumpida.

REFERENCES

1. a) Tietze LF., Beifuss U. *Angew. Chem.*. 1993, *105*, 137; b) Tietze LF. *Chem. Rev*. 1996, *96*, 115.
2. a) Knunyants IL., Bargamova MD. *Izv. Akad. Nauk SSSR, Ser. Khim. (Engl. Transl.)* 1977, 1776; b) Bargamova MD., Motsishkite SM., Knunyants IL. *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* 1990, *39*, 2338.
3. Mc Bee ET., Pierce OR., Kilbourne HW. *J. Am. Chem. Soc*. 1953, *75*, 4091.
4. Haszeldine RN. *J. Chem. Soc*. 1953, 922.
5. Kitazume T., Ohuogi T. *Synthesis* 1988, 614.
6. a) Weygand F., Steglich W., Lengyel I., Fraunberger F., Maierhofer H, Oettmeier W. *Chem. Ber*. 1966, *99*, 1944; b) Burger K., Mütze K., Hollweck W., Koksch B., Kuhl P., Jakubke H-D., Riede J., Schier A. *J. prakt. Chem. / Chem. Ztg*.1993, *335*, 321.
7. a) Kimoto H., Cohen LA. *J. Org. Chem*. 1979, *44*, 2902; b) Kimoto H., Cohen LA. *J. Org. Chem*.1980, *45*, 3831.
8. a) Burger K., Höß E., *Chem. Ztg*. 1989, *113*, 385; b) Burger K., Höß E., Geith K. *Synthesis* 1990, 360.
9. a) Burger K., Ottlinger R., Goth H., Firl J., *Chem. Ber.* 1982, *115*, 2494; b) Burger K., Geith K., Sewald N. *J. Fluorine Chem*. 1990, *46*, 105; c) Burger K., Helmreich B. *J. prakt. Chem. / Chem. Ztg*. 1992, *334*, 311.
10. a) Burger K., Höß E., Sewald N., Geith K., Riede J., Bissinger P., *Z. Naturforsch*. 1990, *45b*, 1695; b) Burger K., Geith K., Höß E. *Synthesis* 1990, 352.
11. Höß E. *PhD, Techn. University Munich*, 1990.
12. work in progress.