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Combined intra–intermolecular criss-cross cycloaddition of a new fluorinated unsymmetrical allenylazine with alkynes

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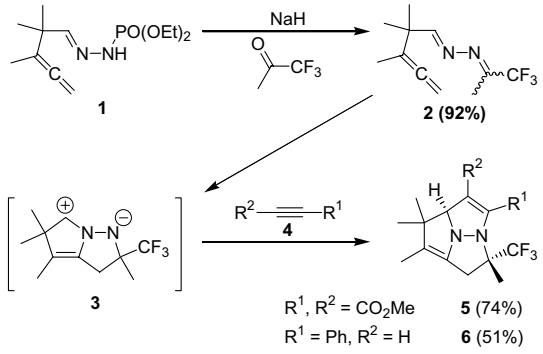
Abstract—The reaction of a new fluorinated unsymmetrical allenylazine with dimethyl acetylenedicarboxylate and phenylacetylene affords the combined intra–intermolecular criss-cross cycloaddition products, 2,3-disubstituted-1,10-diazatricyclo[5.2.1.0^{4,10}]deca-2,6-diene derivatives. The products contain three fused five-membered rings with two nitrogen atoms within an unsaturated heterocyclic system. The structures were assigned using 2D NMR correlations and in the case of the phenylacetylene adduct by X-ray structure analysis.

1. Introduction

Intermolecular criss-cross cycloadditions have been known for a long time.[1] Intramolecular procedures were presented much later. They can lead, depending on dipolarophile regioselectivity, to heterocycles with four fused heterocyclic rings with either central[2] or lateral[3,4] connection of the rings. In the case of combined intra–intermolecular criss-cross additions, heterocycles with three fused five-membered rings are formed. Until now only intra–intermolecular criss-cross additions of unsymmetrical azines [4-methoxybenzaldehyde (2,2,3-trimethylpenta-3,4-dien-1-ylidene)hydrazone and 4-methoxy- benzaldehyde (3-ethyl-2,2-dimethylpenta-3,4-dien-1-ylidene)hydrazone, respectively], with phenylisocyanate had been observed.[5]

2. Results and discussion

In this letter we report that a new fluorinated unsymmetrical azine **2** is able to react with other dipolarophiles (Scheme 1). Thus, substituted acetylenic derivatives **4** react with azine **2** with formation of the new unsaturated fused heterocycles **5** and **6** consisting of three nitrogen-containing five-membered rings.



Scheme 1. Preparation of allenylazine **2** and its criss-cross cycloaddition reactions.

In order to prepare fluorinated azine **2** it was first necessary to prepare 2,2,3-trimethylpenta-3,4-dienal via a Claisen–Cope rearrangement.[6] In order to avoid formation of the symmetrical azine one of the nitrogen atoms of the reacting hydrazine monohydrate was blocked by formation of diethyl hydrazidophosphate.[7] This was then reacted with 2,2,3-trimethylpenta-3,4-dienal to afford **1**. In the following reaction

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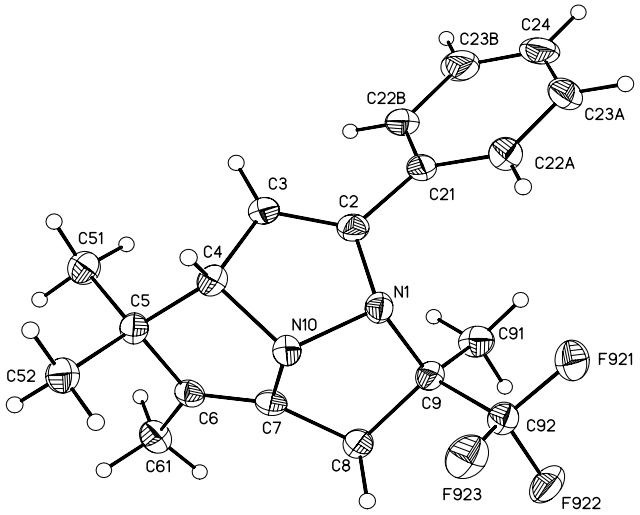

Figure 1. X-ray structure of compound **6**.

with 1,1,1-trifluoroacetone, unsymmetrical azine **2** was obtained in high yield. In comparison with the preparation of similar known derivatives,[6] the reaction time had to be substantially prolonged. On the other hand the azine **2** was stable and no decomposition even at room temperature was observed over several weeks. Its configuration has not yet been determined.

The criss-cross cycloaddition reaction was carried out in dry boiling xylene. This reaction is the first example not involving exclusively an aldazine and having an aliphatic ketone bound on one side. Earlier reactions were observed using aromatic aldazines only with our exception using an homoallenyl aldazine already published.[2] We presume that the reaction proceeds in accordance with our previous experiments,[5] a process involving intramolecular attack via dipolar intermediate **3**. Formation of such a product was also predicted from quantum chemistry calculations.[8] The course of the reaction was monitored by ^{19}F NMR spectroscopy. The reaction was stopped at about 80% conversion, prolonging the reaction led to only a negligible increase in conversion along with formation of decomposition products. Also in this cycloaddition reaction the reaction time is longer compared to aldazine derivatives.[5] Criss-cross addition products **5** and **6** were purified by preparative TLC and their structures were elucidated by 2D NMR. In the case of unsymmetrical alkyne addition, compound **6** was isolated as the main regioisomer. Its lower yield was probably due to the lower reactivity of the dipolarophile (no electron-withdrawing group) and consequently due to decomposition of primary formed intermediate **3**. Reaction with diphenylacetylene failed. The relative configuration of the stereogenic centres was determined by X-ray analysis (see Fig. 1).[9] Also, in the case of product **5** only one diastereoisomer was found having the same configuration as the product **6**. Probably, due to the fact that the trifluoromethyl group is bulkier than the methyl group, the formation of only one diastereoisomer, having the trifluoromethyl directing out of the heterocyclic ring, was observed.

3. Experimental

3.1. *N* -(2,2,2-Trifluoro-1-methylethylidene)-*N*′-(2,2,3-trimethylpenta-3,4-dienylidene)hydrazine (2)

A mixture of diethyl (2,2,3-trimethyl-3,4-pentadienylidene)hydrazidophosphate **1** (3.62 g, 13.2 mmol) and 1,1,1-trifluoroacetone (1.79 g, 16 mmol) in benzene (20 mL) was slowly added to a suspension of NaH (0.48 g, 20 mmol) in benzene (20 mL) at 10 °C. The reaction mixture was left to stir overnight at room temperature. Then the solution was filtered and the residue washed with Et_2O (3 × 15 mL). The combined organic phases were concentrated in vacuo and the crude product was purified by chromatography on silica gel (eluent: CH_2Cl_2) to give azine **2** (2.81 g, 92 %). δ_F ($CDCl_3$) 235 MHz: −73.3 (s); δ_H ($CDCl_3$) 250 MHz: 1.28 (s, 6 H, $(H_3C)_2$–C), 1.69 (t, $^5J_{H,H}$ = 3.1, 3H, CH_3–C═), 2.10 (s, 3H, H_3C–C–CF_3), 4.72 (q, $^5J_{H,H}$ = 3.1, 2H, H_2C═), 7.40 (s, 1H, HC═N); δ_C ($CDCl_3$) 63 MHz: 12.1 (s, H_3C–C–CF_3), 15.2 (s, CH_3–C═), 24.1 (s, $(H_3C)_2$–C), 40.9 (s, $(H_3C)_2$–*C*), 76.2 (s, ═CH_2), 102.8 (s, CH_3–*C*═), 120.7 (q, $^1J_{C,F}$ = 275.1, CF_3), 153.0 (q, $^2J_{C,F}$ = 33.1, F_3C–*C*), 167.1 (s, HC═N), 206.5 (s, ═C═); IR (film) ν_{max}/cm^{-1} 1124, 1198, 1353, 1618, 1660, 1954 (═C═), 2932, 2976. Anal. Calcd for $C_{11}H_{15}F_3N_2$: C, 56.89; H, 6.51; N, 12.06. Found: C, 56.92; H, 6.41; N, 11.65.

3.2. Preparation of compounds 5 and 6

A mixture of fluorinated azine **2** (116 mg, 0.5 mmol) and alkyne **4** (1.0 mmol) in dry xylene (10 mL) was heated under reflux for 16.5 h and then xylene was removed under vacuum. The residue was separated by preparative TLC on silica gel (eluent: CH_2Cl_2 for **5** and AcOEt–pet. ether (10/90) for **6**). The products were crystallized from ether.

3.3. (4*R*,9*R*)-Dimethyl-5,5,6,9-tetramethyl-9-trifluoromethyl-1,10-diazatricyclo[5.2.1.0^{4,10}]deca-2,6-diene-2,3-dicarboxylate (5)

Yield: 74%; mp 89.0–91.5 °C; δ_F ($CDCl_3$) 235 MHz: −80.9 (s); δ_H ($CDCl_3$) 250 MHz: 1.06 (s, 3H, H_3C–C–CH_3), 1.28 (s, 3H, H_3C–C–CH_3), 1.47 (s, 3H, H_3C–C–CF_3), 1.56 (d, $^5J_{H,H}$ = 1.6, 3H, H_3C–C═), 2.37 (d, $^2J_{H,H}$ = 14.6, 1H, CH_2), 2.93 (dq, $^2J_{H,H}$ = 14.6, $^5J_{H,H}$ = 1.6, 1H, CH_2), 3.68 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.39 (s, 1H, CH); δ_C ($CDCl_3$) 63 MHz: 8.3 (s, H_3C–C═), 19.5 (q, $^3J_{C,F}$ = 2.5, H_3C–C–CF_3), 21.3 (s, H_3C–C–CH_3), 28.2 (s, H_3C–C–*C*H_3), 34.1 (q, $^3J_{C,F}$ = 0.7, CH_2), 51.7 (s, OCH_3), 53.2 (s, OCH_3), 55.6 (s, H_3C–*C*–CH_3), 71.0 (q, $^2J_{C,F}$ = 29.7, *C*–CF_3), 76.3 (s, CH), 112.3 (s, H_3C–*C*═), 118.2 (s, HC–*C*═), 125.6 (q, $^1J_{C,F}$ = 281.6, CF_3), 138.7 (s, H_2C–*C*═), 148.0 (s, HC–C═*C*), 163.7 (s, C═O), 164.0 (s, C═O); GC–MS *m*/*z* (%) 374 (M^+, 37), 245 (15), 190 (22), 175 (34), 153 (38), 121 (100); IR (KBr) ν_{max}/cm^{-1} 1350, 1438, 1604, 1702 (C═O), 1739 (C═O), 2864, 2959, 3004. Anal. Calcd for $C_{17}H_{21}F_3N_2O_4$: C, 54.54; H, 5.65; N, 7.48. Found: C, 54.68; H, 5.54; N, 7.11.

3.4. (4*R*,9*S*)-2-Phenyl-5,5,6,9-tetramethyl-9-trifluoromethyl-1,10-diazatricyclo[5.2.1.$0^{4,10}$]deca-2,6-diene (6)

Yield: 51%; mp 139.5–142.5 °C; δ_F ($CDCl_3$) 235 MHz: −80.4 (s); δ_H ($CDCl_3$) 250 MHz: 1.04 (s, 3H, H_3C–C–CF_3), 1.08 (s, 3H, H_3C–C–CH_3), 1.25 (s, 3H, H_3C–C–CH_3), 1.58 (d, $^5J_{H,H}$ = 1.7, 3 H, H_3C–C═), 2.21 (d, $^2J_{H,H}$ = 14.6, 1H, CH_2), 2.90 (dq, $^2J_{H,H}$ = 14.6, $^5J_{H,H}$ = 1.6, 1H, CH_2), 4.21 (d, $^3J_{H,H}$ = 2.3, 1H, *H*C–HC═), 4.80 (d, $^3J_{H,H}$ = 2.3, 1H, HC–*H*C═), 7.2–7.5 (m, 5H, Ph); δ_C ($CDCl_3$) 63 MHz: 8.4 (s, H_3C–C═), 21.3 (q, $^3J_{C,F}$ = 1.5, H_3C–C–CF_3), 21.8 (s, H_3C–C–CH_3), 27.3 (s, H_3C–C–CH_3), 33.8 (q, $^3J_{C,F}$ = 1.1, H_2 *C*–C–CF_3), 52.5 (s, H_3C–*C*–CH_3), 70.8 (q, $^2J_{C,F}$ = 28.2, *C*–CF_3), 78.0 (s, H*C*–HC═), 128.1 (s, CH), 108.8 (s, HC–H*C*═), 116.6 (s, H_3C–*C*═), 126.8 (s, 2 × CH), 126.9 (q, $^1J_{C,F}$ = 281.7, CF_3), 128.4 (s, 2 × CH); 135.4 (s, C), 140.4 (s, H_2C–*C*═), 147.5 (s, *C*–Ph), IR (KBr) ν_{max}/cm^{-1} 1145, 1185, 1332, 1463, 1489, 1598, 1625, 2865, 2926, 2965, 3072; GC–MS *m/z* (%) 334 (M^+, 100), 319 (30), 265 (28), 237 (51), 223 (41), 114 (84), 121 (45). HRMS: calcd. for $C_{19}H_{22}F_3N_2^+$: 335.1735, found: 335.1739.

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