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New fused heterocycles by combined intra-intermolecular criss-cross cycloaddition of nonsymmetrical azines[†]

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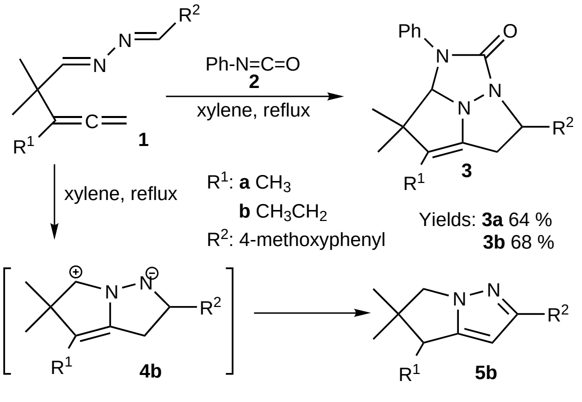
Abstract—Thermally induced intra-intermolecular criss-cross cycloaddition of nonsymmetrical azines in the presence of phenyl isocyanate is described. This one-pot reaction gives heterocyclic compounds containing three fused five-membered rings. The molecular and crystal structure of the products is reported and discussed. © 2002 Elsevier Science Ltd. All rights reserved.

In this paper, the first criss-cross cycloadditions (CCCs) combining both intra- and intermolecular approaches are presented. CCCs are two consecutive 1,3-dipolar cycloaddition reactions of heterodienes most often azines with dipolarophiles. Intermolecular examples of such reactions, resulting in heterocycles with two fused five-membered rings, have been known for a long time.[1] Intramolecular CCCs were presented much later. Generally they can lead, depending on dipolarophile regioselectivity, to heterocycles with four fused rings either with central[2] or lateral[3,4] connection of the rings. In the case of combined intra-intermolecular CCC reactions, heterocycles with three fused five-membered rings are formed.



Scheme 1.

In our previous study[2] we showed that symmetrical azines from 3-alkyl-2,2-dimethylpenta-3,4-dienals are very good substrates for intramolecular CCCs. We decided to prepare similar azines **1** containing only one allenyl dipolarophile in the molecule. For their preparation we protected one of the hydrazine nitrogen atoms against symmetrical azine formation.[5,6] This method always gave better yields than reaction of 3-alkyl-2,2-dimethylpenta-3,4-dienal with one molecule of hydrazine because of the instability of nonprotected hydrazone. Starting 3-alkyl-2,2-dimethylpenta-3,4-dienals were prepared by Claisen–Cope rearrangement.[6] As the second dipolarophile for CCC in the intermolecular step, phenyl isocyanate **2** was used. Desired intra-intermolecular criss-cross cycloadducts **3** were then formed in good yields by heating compounds **1** and **2** together (Scheme 1).

The reaction might have been complicated by a simple intermolecular CCC where two molecules of phenyl isocyanate **2** are added to one molecule of azine **1**, but in our case no trace of such a CC cycloadduct was found in the crude reaction mixture. In an experiment where azine **1b** was heated under similar conditions but without phenyl isocyanate **2**, compound **5b** was isolated. Product **5b** may be a transformation product of a dipolar species **4b** which would be the result of an intramolecular cycloaddition in **1b**. The structure of **5b** indicates that the first step of the CCCs is probably intramolecular formation of dipole **4** followed by intermolecular cycloaddition with phenyl isocyanate **2**.

Keywords: criss-cross cycloaddition; 1,3-dipolar; nonsymmetrical azine; 1,3,10-triazatricyclo[5.2.1.0^{4,10}]dec-6-en-2-one.

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[†] Dedicated to Professor Dr. Jaroslav Jonas on the occasion of his 65th birthday.

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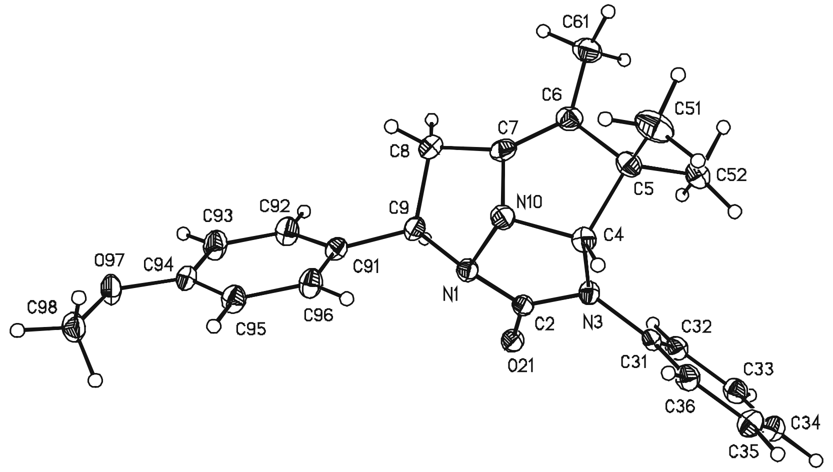

Figure 1. X-Ray structure of compound **3a**.

The structures of compounds **3** were solved by NMR spectra as well as by X-ray analysis. Formation of only one diastereoisomer was observed. The structure **3a** is depicted in Fig. 1. All the bond and angle parameters are within the ranges normally expected.

Our method represents an easy way for preparation of a new class of compounds with three fused five-membered nitrogen containing rings. It combines both intra- and intermolecular types of criss-cross cycloaddition.

Experimental

NMR spectra were measured at Bruker Avance DRX 300, FT IR spectra at GENESIS ATI (Unicam), MS at MS TRIO 1000 (Fisons), crystallographic data for structures have been deposited at the Cambridge Crystallographic Data Centre. Compounds **1** were prepared according to the literature.[6]

A nonsymmetrical azine **1a** or **1b** (1.5 mmol) was mixed with phenyl isocyanate **2** (1.5 mmol) in dry xylene (50 cm^3) under argon. The mixture was heated to reflux for 2 h, then xylene was removed under vacuum. The residue was mixed with diethyl ether and the precipitate formed was collected and washed with petroleum ether and dried.

3-Phenyl-9-(4-methoxyphenyl)-5,5,6-trimethyl-1,3,10-triazatricyclo[5.2.1.0^{4,10}]dec-6-en-2-one (3a): Crystallization from ethanol gave 64% of **3a**; mp 164–168°C; δ_H ($CDCl_3$) 0.77 (3H, s, CH_3C), 1.30 (3H, s, CH_3C), 1.52 (3H, d, $J=1.9$, CH_3-C=), 2.52 (1H, dm, $J=15.2$, CH_2-C=), 3.12 (1H, dd, $J_1=15.2$, $J_2=9.0$, CH_2-C=), 3.79 (3H, s, CH_3-O), 5.30 (1H, dd, $J_1=9.0$, $J_2=5.4$, CH_2-$C\underline{H}$-N), 5.49 (1H, s, CH-N), 6.8–7.3 (9H, m, Ar.H); δ_C ($CDCl_3$) 8.4, 21.9, 25.5, 32.1, 55.33, 55.35, 64.7, 84.5, 114.0, 115.9, 122.6, 125.2, 127.3, 128.9, 135.3, 139.1, 143.1, 158.8, 161.9; IR (KBr) ν_{max}/cm^{-1} 699, 825, 1029, 1170, 1250, 1296, 1409, 1511, 1598, 1703 (C=O), 2927, 2964, 3019, 3061; MS (EI 30 eV) m/z (%) 375 (M^+, 33), 280 (31), 268 (52), 241 (19), 213 (17), 162 (100), 134 (55), 122 (20), 108 (25), 91 (27), 77 (70); X-ray: CCDC number 179018.

6-Ethyl-3-phenyl-9-(4-methoxyphenyl)-5,5-dimethyl-1,3,10-triazatricyclo[5.2.1.0^{4,10}]dec-6-en-2-one (3b): Crystallization from ethanol gave 68% of **3b**; mp 156–158°C; δ_H ($CDCl_3$) 0.80 (3H, s, CH_3C), 1.08 (3H, t, $J=7.6$, $C\underline{H}_3$-CH_2), 1.36 (3H, s, CH_3C), 1.99 (2H, m, CH_3-$C\underline{H}_2$), 2.60 (1H, dd, $J_1=15.5$, $J_2=5.0$, CH_2-C=), 3.22 (1H, dd, $J_1=15.2$, $J_2=8.9$, CH_2-C=), 3.81 (3H, s, CH_3O), 5.34 (1H, dd, $J_1=8.9$, $J_2=5.0$, CH_2-$C\underline{H}$-N), 5.46 (1H, s, CH-N), 6.8–7.4 (9H, m, Ar. H); δ_C ($CDCl_3$) 13.7, 17.6, 22.2, 26.5, 32.8, 55.4, 55.8, 64.7, 84.8, 114.1, 121.4, 122.8, 125.4, 127.4, 128.9, 135.4, 139.2, 143.0, 158.9, 162.1; IR (KBr) ν_{max}/cm^{-1} 760, 827, 1030, 1169, 1221, 1244, 1296, 1383, 1512, 1597, 1709 (C=O), 2931, 2970, 2983; MS (EI 30 eV) m/z (%) 389 (M^+, 27), 280 (38), 270 (15), 255 (11), 241 (12), 227 (17), 162 (100), 134 (29), 104 (28), 91 (25), 77 (69); X-ray: CCDC number 179017.

Azine **1b** when heated in xylene to reflux for 2 h afforded after removal of xylene a liquid identified as compound **5b**.

4-Ethyl-2-(4-methoxyphenyl)-5,5-dimethyl-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole (5b): δ_H ($CDCl_3$) 1.09 (3H, s, CH_3C), 1.14 (3H, t, $J=7.4$, $C\underline{H}_3CH_2$), 1.22 (3H, s, CH_3C), 1.42 (1H, m, $CH_3C\underline{H}_2$), 1.62 (1H, m, $CH_3C\underline{H}_2$), 2.65 (1H, dd, $J_1=10.6$, $J_2=4.6$, $C\underline{H}$-CH_2), 3.78 (3H, s, CH_3-O), 3.81 (1H, d, $J=10.6$, C-CH_2-N), 3.88 (1H, d, $J=10.6$, C-CH_2-N), 6.23 (1H, s, C=CH-C), 6.92 (2H, d, $J=6.9$, Ar.H), 7.74 (2H, d, $J=6.9$, Ar.H); δ_C ($CDCl_3$) 12.8, 21.7, 22.8, 27.6, 45.9, 49.8, 55.3, 60.9, 96.4, 114.0, 126.6, 127.3, 150.0, 154.7, 159.1.

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