Adducts of Tröger bases and activated acetylenes: synthesis and structure☆

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Abstract—It was found by X-ray diffraction and NMR studies that the structure of the adduct of bis-*ortho*-methyl-bis-*para*-methyl substituted Tröger base and dimethyl acetylenedicarboxylate is a [3.3.1]bicyclic compound corresponding to the methyl 13-[1-(methoxycarbonyl)vinyl]-13-carboxylate. Chemical and NMR evidence supported similar structures for all other reported adducts of Tröger bases and activated acetylenes.
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Tröger bases (TBs) **1** are inherently chiral heterocycles with a saturated bicyclic core (highlighted).[2] The chemical properties of TBs can be divided into the reactions of the saturated core and those of the aromatic moieties. Aromatic reactions are non-specific and include, for example, Pd-catalyzed cross-coupling.[3] Reactions of the bicyclic core include racemization[4] and diastereomerization[5] in the presence of acids, N-mono- and dialkylation,[6] benzylic C-lithiation in the presence of BF₃ and then C-alkylation,[7] and reactions with loss of the methano-bridge. Thus, TBs can be di-N-acylated, di-N-nitrosylated[8] or converted into ethano-TBs[9] with loss of formaldehyde.
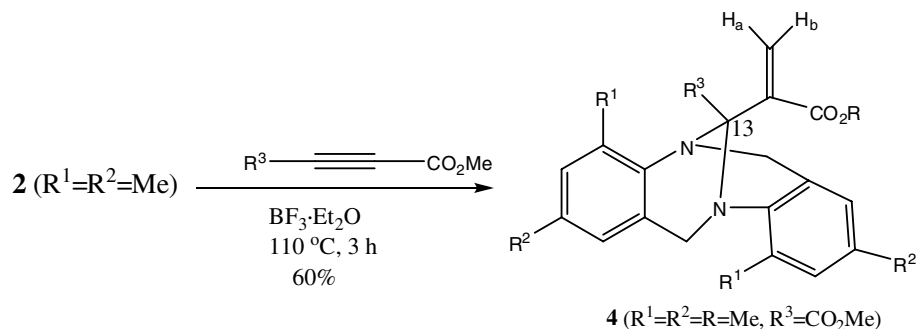

1
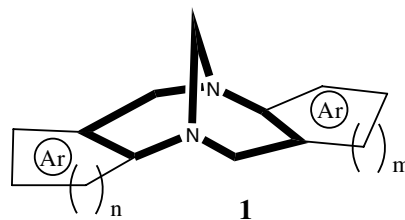
It has been reported recently that the parent TB **2** (R¹ = H, R² = Me)[10] reacts with activated acetylenes in the presence of ZnBr₂ in MeCN to give [3.3.3]bicyclic products **3** (Scheme 1).[11] We were eager to study this
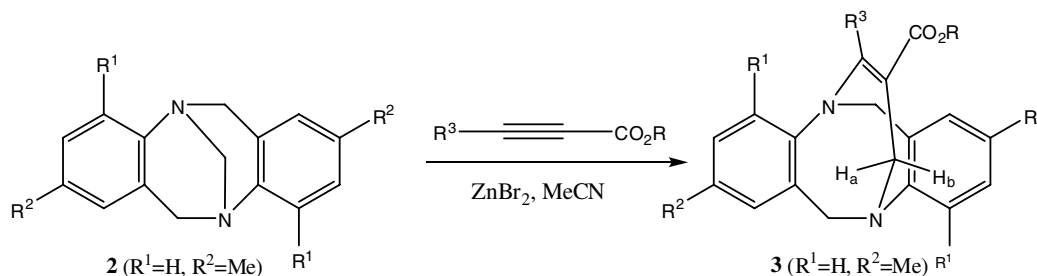
Scheme 1.

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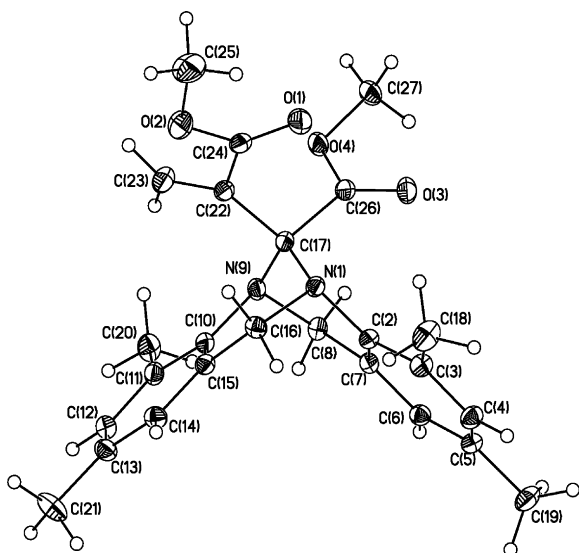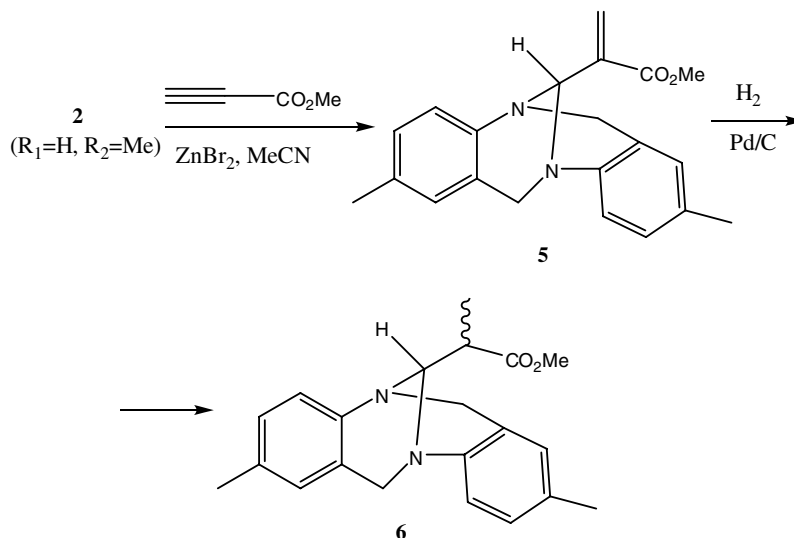

Scheme 2.

Figure 1. Projection of the X-ray crystal structure of compound **4** ($R^1 = R^2 = R = Me$, $R^3 = CO_2Me$).

reaction with bis-*ortho*-methyl substituted TBs **2** ($R^1 = Me$) in order to investigate the effect of substitu-

ents. We found that bis-*ortho*-substitution makes TBs practically inert to racemization in acidic media.[4f–h] Furthermore, it has been shown recently that an analogous effect of bis-*ortho*-substitution is observed for diastereo-merization of TBs.[5d]

The reaction of TB **2** ($R^1 = R^2 = Me$) with dimethyl acetylenedicarboxylate in the presence of $BF_3 \cdot Et_2O$ gave a product, to which we assigned the structure as methyl 13-[1-(methoxycarbonyl)vinyl]-13-carboxylate **4** ($R^1 = R^2 = R = Me$, $R^3 = CO_2Me$) (Scheme 2).[12] The assignment of structure **4** was based on ^1H NMR[12] and X-ray diffraction data[13] (Fig. 1).

The isomeric structures **4** and **3** contradict each other. We turned our attention to the original publication on the synthesis of compounds **3** to analyze if the reactivity of TB **2** ($R^1 = R^2 = Me$) had been affected by the different substitution or the use of different Lewis acid and whether structure **3** was correct. We looked at the chemical shifts of the protons H_a and H_b (Schemes 1 and 2). In compound **4** ($R^1 = R^2 = R = Me$, $R^3 = CO_2Me$) and compound **3** these protons are in the region of 6 ppm, which is appropriate for protons of unsaturated bonds but very unusual for allylic protons. Moreover, the expected geminal H_aH_b-coupling constants for **3** were

Scheme 3.
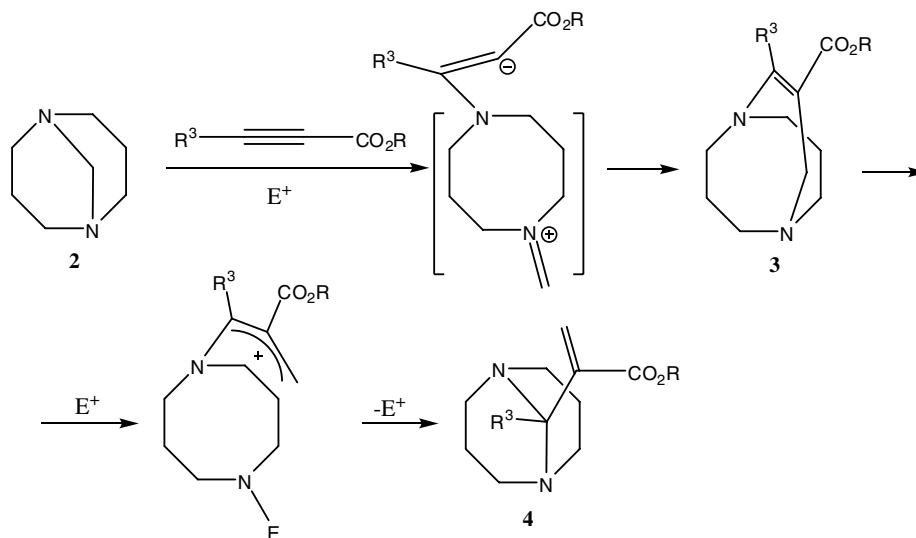
Scheme 4. The proposed mechanism of formation of the adducts of TBs and activated acetylenes (only saturated regions of the molecules are shown).

absent, whereas in **4** ($R^1 = R^2 = R = Me$, $R^3 = CO_2Me$) $^2J = 0.9$ Hz, which is typical for methylene double bond protons, but unprecedented for protons at an sp^3-carbon. Therefore, we conclude that the [3.3.3]bicyclic structure **3** is incorrect and should be substituted by the [3.3.1]bicyclic structure **4**. The chemical reactivity of the adduct between methyl propiolate and TB **2** ($R^1 = H$, $R^2 = Me$) (**5**, Scheme 3), studied by the same authors,[11] supported our conclusion. Thus, compound **5** was hydrogenated to give the diastereomeric mixture **6** (Scheme 3).

The mechanism for the formation of products **4** may involve an allylic rearrangement promoted by the Lewis acid (Scheme 4).

Acknowledgements

References and notes

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12. Compound **4** ($R^1 = R^2 = R = Me$, $R^3 = CO_2Me$) was obtained from compound **2** ($R^1 = R^2 = Me$)[6a] (1 mmol), dimethyl acetylenedicarboxylate (1 mmol) and BF$_3$·Et$_2$O

(1 mmol) by heating at 110 °C in a sealed ampoule for 3 h. The reaction mixture was dissolved in CH_2Cl_2 (10 ml) and shaken with satd Na_2CO_3. The solvent was evaporated and the residue chromatographed on SiO_2 (EtOAc/petroleum ether). Yield 60%. Mp 167–168 °C (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm, J, Hz: 2.16 (s, 6H, 2Me), 2.38 (s, 3H, Me), 2.44 (s, 3H, Me), 3.65 (s, 3H, OMe), 3.76 (s, 3H, OMe), 3.83 (d, $^2J = 17.0$, 1H), 3.93 (d, $^2J = 17.5$, 1H), 4.20 (d, $^2J = 17.5$, 1H), 4.36 (d, $^2J = 17.0$, 1H), 5.87 (br s, 1H, C=CH$_{a(b)}$), 6.00 (d, $^2J = 0.9$, 1H, C=CH$_{b(a)}$), 6.44 (s, 2H, H(Ar)), 6.86 (s, 2H, H(Ar)).

13. *Crystallographic data:* Crystals of **4** ($R^1 = R^2 = R = Me$, $R^3 = CO_2Me$) ($C_{25}H_{28}N_2O_4$, M = 420.49) are monoclinic, space group $P2_1/c$, at 100(2) K: $a = 14.9601(8)$, $b =$ 14.3875(8), $c = 10.1669(6)$ Å, $\beta = 99.204(5)°$, $V = 2160.1(2)$ Å^3, $Z = 4$, $d_{calc} = 1.293$ g cm^{-3}. Intensities of 27,822 reflections were measured with a 'Smart APEX2' diffractometer (ω-scans, $\theta < 30.0°$) and 18,052 independent reflections were used in further refinement. The refinement converged to $wR2 = 0.1281$ and GOF = 1.027 for all independent reflections ($R1 = 0.04712$ was calculated against F for 5227 observed reflections with $I > 2\sigma(I)$. The crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, CCDC-631875. Copies of this information may be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).