New synthesis of (*Z*,*E*)-2,7-bis(4-cyanobenzylidene)cycloheptan-1-one under stereospecific constraints induced by host–guest interactions†

Arnaud Grandeury,[a] Samuel Petit,[b] Servane Coste,[b] Gérard Coquerel,[b] Cécile Perrio[c] and Géraldine Gouhier*[d]

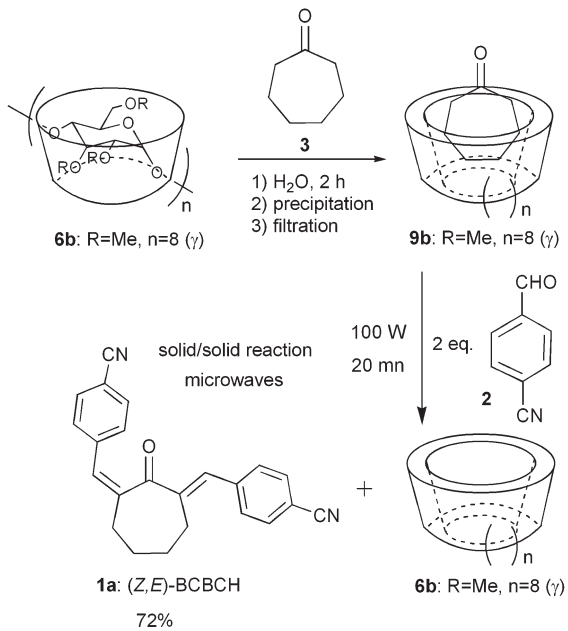
Received (in Cambridge, UK) 12th April 2005, Accepted 13th June 2005
First published as an Advance Article on the web 12th July 2005
DOI: 10.1039/b504989j

A selective, efficient, and fast access to (*Z,E*)-2,7-bis(4-cyanobenzylidene)cycloheptan-1-one (BCBCH), precursor of the synthetic antagonist of tissue-plasminogen activator (t-PA), is reported using a solid/solid aldolisation–crotonisation reaction on a supramolecular complex under microwave irradiation. The underlying mechanism is investigated from the crystal structure of the intermediate host–guest complex formed between permethylated γ-cyclodextrin and (*Z*)-2-(4-cyanobenzylidene)cycloheptan-1-one.

Serine proteases have been extensively studied to elucidate coagulation and thrombolysis processes. In addition to their existence in the blood, several of these proteases have been localized within the central nervous system (CNS). In the brain, one of the most frequently studied serine protease is the tissue-plasminogen activator (t-PA) which plays a key role in the homeostasis of the CNS. It is known that 2,7-bis(4-amidinobenzylidene)cycloheptan-1-one (BABCH) isomers are synthetic antagonists of t-PA.[1] Their ability to interact with one of the t-PA catalytic sites is exploited to understand the enzymatic activity and the role of t-PA in the CNS.[2] But at the present time, syntheses of these inhibitors are neither selective (mixture of isomers) nor efficient (4%, 3 steps).[1] Therefore we focused our research work on the development of new synthesis routes. While doing so, a new methodology was developed to obtain selectively a precursor of the (*Z,E*)-BABCH: the (*Z,E*)-2,7-bis(4-cyanobenzylidene)cycloheptan-1-one (BCBCH) **1a**. According to the literature, both (*Z,E*) **1a** and (*Z,Z*)-BCBCH **1b** can be obtained with 18% and 22% yields respectively, in two steps by condensation of 4-cyanobenzaldehyde **2** with cycloheptanone **3**[3] followed by a photoisomerisation reaction to give a mixture of isomers (*Z,E*) **1a**, (*Z,Z*) **1b**, (*E,E*) **1c** in a ratio 45:50:5.[1] In order to improve the selectivity of this reaction, a strategy based on supramolecular host–guest interactions has been developed. The inclusion geometry of the guest molecule had to allow the aldolisation–crotonisation process and to keep stable under reaction conditions. For this purpose, cyclodextrins (Cds) were selected as macrocyclic hosts. Cds are natural cyclic oligosaccharides consisting of 6, 7, or 8 α-(1–4)-linked D-glucose units, known as α, β and γCds.[4] Their annular shape allows the complete or partial insertion of a large variety of molecules, and permits the solubilization of organic compounds in aqueous medium. Moreover, native Cds can be easily functionalized in order to modulate or modify their properties. For example, permethylated Cds (PM-Cds)[5] exhibit a larger molecular flexibility and their complexes present a retrograde solubility in water (*i.e.*, the solubility is decreased upon heating).

In this study, six macrocycles were tested with different size and substitution: natives α, β, γCd **4a**, **5a**, **6a** (R = H) and α, β, γPM-Cds **4b**, **5b**, **6b** (R = Me) respectively (Scheme 1).

First, the starting material, *i.e.* inclusion complexes formed between **4a–b**, **5a–b**, **6a–b** and **3** were crystallized from aqueous solutions,† and stoichiometries were determined by ^{1}H-NMR spectrometry. The complex **7a** (**4a**:**3**) showed a 2:1 host–guest



Scheme 1 Synthesis of (*Z,E*)-BCBCH **1a** in two steps

[a]*Max-Planck-Institut für Dynamic komplexer technischer Systeme, Sandorstraße 1, D-39106, Magdeburg, Germany*
[b]*UPRES EA 3233, SMS, IRCOF, Université de Rouen, 1 Rue Tesnière, F-76821, Mont Saint Aignan cedex, France*
[c]*UMR CEA, Centre Cycéron, Bd H. Becquerel, BP 5229, F-14074, Caen Cedex, France*
[d]*UMR CNRS 6014, LFAOC, IRCOF, Université de Rouen, 1 Rue Tesnière, F-76821, Mont Saint Aignan cedex, France. E-mail: geraldine.gouhier@univ-rouen.fr; Fax: (+33) 2 35 52 29 71; Tel: (+33) 2 35 52 24 67*

† Electronic supplementary information (ESI) available: general procedure to form crystalline complexes with Cds; crystal structure determination; synthesis and physical data of **1a**, **1c**, **10a–b** and **11**; XRPD pattern of complexes **7a–b**, **8a–b**, and **9a–b**; ^{1}H NMR Spectrometries of **10a–b** and **11**. See http://dx.doi.org/10.1039/b504989j

ratio, whereas a 1:1 stoichiometry was established for all other complexes **7b** (**4b**:**3**), **8a–b** (**5a–b**:**3**) and **9a–b** (**6a–b**:**3**). We assumed that the lipophilic cycle stood inside the cavity and that the ketone function was localized on the upper part of the macrocycle, in the more hydrophilic area (ref. 6 and ref. therein). Therefore, **3** could be submitted to an important steric constraint, but its reactive site could be still accessible to envisage an organic reaction.

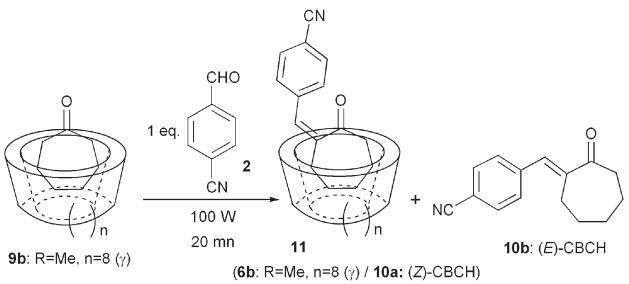
To avoid side mechanisms, the reaction conditions have been chosen in order to fulfil two conditions: i. Presence of water should be avoided due to the reversible aldol condensation; ii. Organic solvent are well-known to shift the host–guest equilibrium in Cd chemistry, and are not suitable to preserve the stereospecific constraints. Therefore, the condensation was carried out without solvent under microwave (MW) irradiation.[7] The reaction was first optimized in heterogeneous phase with **3** (liquid) and **2** (solid) and catalyzed under various MW irradiation conditions. The (*E,E*)-isomer **1c** was obtained with 74% yield after simple filtrations and washings. These conditions were applied to the supramolecular complexes, but no reaction occurred, probably due to the solid/solid medium. Harder conditions with 0.4 equivalent of *p*-toluenesulfonic acid (PTSA) at 100 W for 20 minutes allowed the reaction (Scheme 1). ^{1}H NMR Analysis of reacting mixtures revealed the disappearance of supramolecular interactions. Formation of **1c** was observed in all cases except with **6b** for which selectively **1a** was obtained with 72% isolated yield. No degradation reactions of **4a–b**, **5a–b**, **6a–b** were detected and **6b** was totally recovered by flash chromatography. In order to understand the underlying mechanism, the inclusion ability of the monosubstituted product was investigated. Thus, following a similar procedure, the monocondensation of **2** in the presence of **9b** led to a mixture of (*Z*)-CBCH **10a** and (*E*)-CBCH **10b** in a ratio 95:5 (*Z*/*E*) with 57% yield (Scheme 2).†

Compound **10a** appears engulfed into **6b** forming a new inclusion complex **11**. No complex was observed when this reaction was carried out with **7a–b**, **8a–b**, and **9a**; in these cases, only the *E* isomer and the free macrocycles **4a–b**, **5a–b**, and **6a** were detected.

Structural investigation on a single crystal of complex **11** was attempted,‡ allowing the first structure determination of an inclusion complex formed between an organic molecule and **6b**.

In the literature, few structural data with **6b** are available, corresponding only to different hydrated forms. Among the known structures, two of them exhibit an identical and unusual conformation of the crown with an elliptically bowl-shaped structure.[8a,b] In the third one, **6b** is almost circular with 4.5 water molecules engulfed in the cavity.[8c] Surprisingly, our structural data present the same parameters as those described by Saenger and coworkers[8c] despite the important volume difference between the guests. Indeed, the superimposition of these structures revealed identical features in terms of macrocycle conformations and crystal packings. Regarding the inclusion geometry, **10a** is engulfed in the macrocycle and only the cyanobenzyle group protrudes from the cavity (Fig. 1). Although thermal displacement ellipsoids of the guest are rather large at room temperature, this relative orientation of host and guest components was confirmed by a structural analysis performed at 100 K, leading to identical atomic positions with smaller ellipsoids. From this structure, it appears that the *E* geometry of the diene cannot be tolerated with such an inclusion, and the ketone function is hidden behind the methoxy functions of the macrocycle **6b**. As the synthesis occurs in the solid state, this new inclusion geometry can be postulated as the real reaction intermediate, without considering packing features (grinding of the reagent powders was necessary before MW irradiation). Consequently, this new position prevents the second aldolisation reaction. The MW irradiation might therefore eject **10a** from **11** or **3** from **7a–b**, **8a–b** and **9a**, releasing the guest and then allowing the condensation, followed by the reversible loss of water without steric constraint in *E* configuration.[9] The MW irradiation impact on the decomplexation process was studied unsuccessfully by: NMR spectrometry (partial miscibility of **3** in water); XRPD (amorphisation of the reacting powders); IR spectrometry (no significant shift). The absence of selectivity observed with **9a** was probably due to its lower molecular flexibility resulting from intramolecular hydrogen-bonding. It can be postulated that the combination of energetic constraints and steric effects in the presence of activating reagent for the aldolisation reaction could be at the origin of the decomplexation process.

In conclusion, a selective, efficient, and fast access to (*Z,E*)-BCBCH **1a** is reported using a solid/solid aldolisation–crotonisation reaction on a supramolecular complex under MW irradiation. The mechanism was elucidated by X-Ray analysis of the intermediate complex structure **11**. Thus, the target (*Z,E*)-2,7-bis(4-amidinobenzylidene)cycloheptan-1-one (BABCH) can be obtained with a superior pathway than reported in the literature (4%) from (*Z,E*)-2,7-bis(4-cyanobenzylidene)cycloheptan-1-one **1a** with a global yield of 21%. Work is in progress to develop a new



Scheme 2 Synthesis of (*Z*)-CBCH **10a** by monocondensation of 4-cyanobenzaldehyde **2** on complex **9b**: formation of complex **11**.

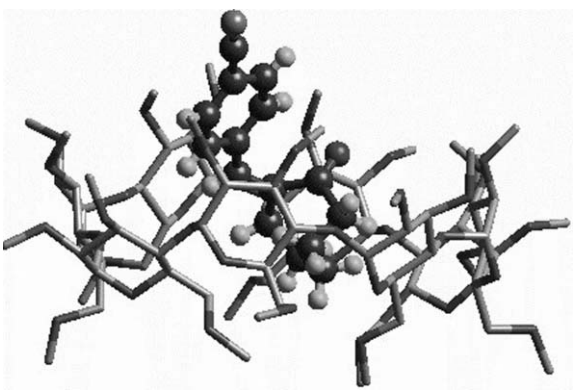


Fig. 1 Profile view of (γPM-Cd **6b**/(*Z*)-CBCH **10a**) complex **11** from crystal structure analysis.†

synthesis of (*Z,Z*)-BABCH using other types of supramolecular interactions.

We are grateful to Haute-Normandie Region *via* the Punchorga network for A. Grandeury's PhD fellowship, and to CRIHAN for providing access to the molecular modelling software Sybyl.

Notes and references

‡ Crystal data of **11**: $C_{72}H_{128}O_{40}.C_{15}H_{15}NO$, M = 1859.02, orthorhombic $P2_12_12_1$, a = 10.819(1), b = 29.413(2), c = 31.945(2) Å, V = 10165(3) Å^3, T = 296 K, Z = 4, μ(Mo–Kα) = 0.1 mm^{-1}, 82138 reflections measured, 11364 unique ($R_{int.}$ = 0.043), Final R indices ($I > 2\sigma(I)$) R_1 = 3.84%, $wR(F^2)$ = 8.81%. A total of 30 restraints (23 distances and 7 angles) have been used during the last refinement steps in order to improve the geometry of cyclic moieties of the guest and that of several methoxy groups of the host. CCDC 264391. See http://dx.doi.org/10.1039/b504989j for crystallographic data in CIF or other electronic format.

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