and Applications in Synthetic Organic Chemistry

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1. Experimental Procedures


Cucurbit[6]uril was prepared and purified according to the procedure described by Day and his group. I$_2$-CB[6] and Br$_2$-CB[6] were prepared by diffusing the halogens vapor trough solid CB[6] in a closed flask. 0.5046 grams (5.066.10$^{-4}$ mol) of CB[6] were placed in a 50 mL beaker. The later was placed in a closed flask containing solid iodine 1000 times excess at room temperature. The same was done using 0.5104 grams (5.124.10-4 mol) of CB[6] and liquid bromine. The solids were exposed to the halogen vapors for a week, and they were revolved daily, in order to guarantee homogeneous gas contact. After this period a coffee-brown solid (I$_2$-CB[6], 0.6776 grams) and a light-orange solid (Br$_2$-CB[6], 1.0484 grams) were collected (Figure SI1). The inclusion compounds were left at open air for 96 hours to remove any excess of halogen that could be weakly bonded or trapped in the solids. The solids were weighted 4 times during this period (see fig. SI2).

Figure SI1. From left to right, pictures of: Bromine inclusion, Br$_2$-CB[6], iodine inclusion, and I$_2$-CB[6].
Figure S12: Desorption isotherms for Iodine and Bromine inclusion compounds, fitted using sigmoidal decay functions.

The solids were weighted again, this time I$_2$-CB[6], 0.6656 grams and Br$_2$-CB[6], 0.8854 grams. These values corresponds to (I$_2$)$_{1.25}$-CB[6] and (Br$_2$)$_{4.25}$-CB[6]. Thermogravimmetry was carried out on a SDT 2960 simultaneous DTA–TGA equipment in O$_2$ atmosphere to confirm these compositions (1 °C/min until 200 °C and 5 °C/min until 700 °C). Pure CB[6] presents 4 decomposition steps, one between 25 and 100 °C, assigned to water loss and 3 others, above 200 °C assigned to the macrocycle decomposition itself (Figure S12). I$_2$ inclusion compound presents an additional weight loss between 100 and 191 °C, which
corresponds to halogen loss (Figure SI3). For bromine it is the same except for the fact that an additional bromine loss is verified at the very beginning of the experiment (temp< 75 °C). It is the adsorbed bromine leaving the sample (Figure SI3).

Data corresponds to CB[6].5 H₂O, (Br₂)₄·₂-CB[6].10H₂O; probably 2.5 Br₂ adsorbed in external halogen bonds and 1.5 included, and (I₂)-CB[6].4H₂O. Apparently no adsorbed iodine is present.

Figure SI3. Thermal decomposition of CB[6].
Figure SI4. Thermal decomposition of Br$_2$-CB[6] and I$_2$-CB[6].

1.2.1. General information

All commercially available reagents were used without further purification unless otherwise noted. CH$_2$Cl$_2$ was freshly distilled over CaH$_2$. MeOH was dried by refluxing with magnesium turnings. TLC analyses were performed in silica gel plates, using UV and/or $p$-anisaldehyde solution for visualization. Flash column chromatography was performed using silica gel 200-400 Mesh. Melting points are uncorrected. All NMR analyses were recorded using CDCl$_3$ as solvent and TMS internal pattern.

1.2.2. Iodine Catalyzed Prins Cyclization$^2$

To a stirred solution of alkenol 1 (0.113 g, 0.600 mmol) and diethyl ketone 2 (0.06 mL, 0.6 mmol) in CH$_2$Cl$_2$ (5 mL), was added I$_2$ (0.030, 0.076 mmol). The mixture was refluxed for 3 h. Na$_2$SO$_3$ (0.0104 g, 0.076 mmol) and H$_2$O (10 mL) were added. The aqueous phase was extracted with AcOEt (3x5 mL). The combined organic phase was washed with brine (5 mL) and dried over anhydrous MgSO$_4$. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (5% AcOEt in hexanes), affording the product 3$^2$ (0.115 g, 0.450 mmol, 75%) as solid (mp: 58-60 °C).
1.2.3. I$_2$-CB[6] Catalyzed Prins Cyclization

As in 1.2.2, but using alkenol 1 (0.113 g, 0.600 mmol), diethyl ketone 2 (0.059 mL, 0.60 mmol), and I$_2$-CB[6].4H$_2$O (0.016 g, 0.012 mmol). The product 3$^2$ (0.126 g, 0.492 mmol, 82%) was obtained as a colorless solid (mp: 58-60 °C).

1.2.4. Iodine-Catalyzed N-Boc Protection of Benzyl Amine$^3$

To a stirred mixture of benzyl amine 4 (0.11 mL, 1.0 mmol) and of (Boc)$_2$O (0.23 mL, 1.0 mmol) was added a catalytic amount of I$_2$ (0.025 g, 0.10 mmol) under solvent-free conditions at rt. After 15 min, Et$_2$O (10 mL) was added to the reaction mixture. The reaction mixture was washed with aqueous Na$_2$S$_2$O$_3$ (5%, 5 mL) and with saturated NaHCO$_3$ (5 mL). The organic layer was dried over anhydrous MgSO$_4$, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (gradient elution, 5-15% AcOEt in hexane) to afford the product 5 as a colorless solid (0.195 g, 0.943 mmol, 94%). mp: 58-60 °C (Lit.$^4$ 57 °C).

1.2.5. I$_2$-CB[6]-Catalyzed N-Boc Protection of Benzyl Amine

As in 1.2.4, but using benzyl amine 4 (0.11 mL, 1.0 mmol), (Boc)$_2$O (0.23 mL, 1.0 mmol) and I$_2$-CB[6].4H$_2$O (0.053 g, 0.040 mmol). N-boc benzyl amine 5 was obtained as a colorless solid, mp: 57-58 °C (Lit.$^4$ 57 °C) (0.194 g, 0.935 mmol, 93%).
1.2.6. β-Keto enol Etherification of Dimedone with Iodine

To a stirred solution of dimedone 6 (0.140 g, 1.00 mmol) in MeOH (10 mL) was added I$_2$ (0.0076 g, 0.030 mmol). The reaction was monitored by TLC. After the reaction was complete, the solvent was removed under reduced pressure. The residue was extracted with AcOEt (2x5 mL) and washed with aqueous Na$_2$S$_2$O$_3$ (5 mL), with H$_2$O (5 mL), and with brine (5 mL). The organic layer was dried over anhydrous MgSO$_4$, filtered and the solvent was removed under reduced pressure. The product was purified by flash column chromatography (10% AcOEt in hexane) affording the enol ether 7 as a colorless oil (0.136 g, 0.881 mmol, 88%).

1.2.7. β-Keto enol Etherification of Dimedone with I$_2$-CB[6]

As in 1.2.6, but using dimedone 6 (0.140 g, 1.00 mmol), MeOH (10 mL) and I$_2$-CB[6].4H$_2$O (0.016 g, 0.012 mmol) as a catalyst instead of I$_2$. Enol ether 7 as a colorless oil (0.141 g, 0.916 mmol, 92%).

1.2.8. Iodine-Catalyzed Cross-Aldol condensation of cyclohexanone and p-tolylaldehyde

To a stirred solution of p-tolylaldehyde 9 (0.129 mL, 1.10 mmol) and cyclohexanone 8 (0.052 mL, 0.50 mmol) in CH$_2$Cl$_2$ (5 mL) was added I$_2$ (0.038 g, 0.30 mmol). The mixture was stirred at rt. The reaction was monitored by TLC. After completion of the reaction, the mixture was treated with aqueous Na$_2$S$_2$O$_3$ (5 mL) solution.
The aqueous phase was extracted with EtOAc (3x5 mL). The organic layer was dried over anhydrous MgSO$_4$, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (gradient elution, 5-15% AcOEt in hexane) to afford the product 10 as a yellow solid (0.143 g, 0.947 mmol, 95%). mp 172-173 °C (Lit.$^7$ 172-173 °C).

1.2.9. I$_2$-CB[6]-Catalyzed Cross-Aldol Condensation of Cyclohexanone and $p$-Tolylaldehyde

As in 1.2.8, but using $p$-tolylaldehyde 9 (0.129 mL, 1.10 mmol), cyclohexanone 8 (0.052 mL, 0.50 mmol) and I$_2$-CB[6].4H$_2$O (0.053 g, 0.040 mmol). The product 10 was obtained as a yellow solid, mp 170-173 °C (Lit.$^7$ 172-173 °C) (0.112 g, 0.372 mmol, 74%).

1.2.10. Iodine-catalyzed Synthesis of 14-(4-Methylphenyl)-14$H$-dibenzo[a,j]xanthene$^8$

$p$-Tolylaldehyde 9 (0.059 mL, 0.50 mmol), β-naphthol 11 (0.168 g, 1.00 mmol) and I$_2$ (0.0032 g, 0.013 mmol) were ground well and transferred to a 50 mL flat-bottomed flask and heated on a hot plate at 90–95 °C for 50 min. After complete conversion (monitored on TLC), the system was cooled to rt. The mixture was washed with Na$_2$S$_2$O$_3$ (10%, 5 mL) solution and the separated precipitate was purified by recrystallization from aqueous ethanol to afford xanthene 12 as a colorless solid (0.172 g, 0.462 mmol, 92%). mp. 227-229 °C (lit.$^8$ 228 °C).
1.2.11. I$_2$-CB[6]-catalyzed Synthesis of 14-(4-Methylphenyl)-14H-dibenzo[a,j]xanthene.

As for 1.2.10, but using $p$-tolyaldehyde 9 (0.059 mL, 0.50 mmol), $\beta$-naphthol 11 (0.168 g, 1.00 mmol) and I$_2$-CB[6].4H$_2$O (0.0067 g, 0.0051 mmol). Xanthene 12 was obtained as a colorless solid, mp: 229-230 °C (Lit.$^8$ 228 °C) (0.136 g, 0.365 mmol, 73%).

1.2.12. Bromination of Benzene with Br$_2$

To a stirred solution of anhydrous benzene 13 (0.067 g, 0.85 mmol) and anhydrous pyridine (0.0068 ml, 0.085 mmol) was added carefully Br$_2$ (0.0600 mL, 1.16 mmol) at 0 °C. The temperature of the water bath was slowly raised to 65-70 °C. After 15 min, NaOH (10%, 5 mL) was added to the reaction mixture. The aqueous phase was extracted with hexane (2x5 mL) and with water (10 mL). The organic layer was dried over anhydrous MgSO$_4$, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (hexane) to afford bromobenzene 14 as a pale yellow oil (0.072 g, 0.459 mmol, 54%).

1.2.13. Bromination of Benzene with Br$_2$-CB[6]

As in 1.2.12, but using benzene 13 (0.0645 g, 0.820 mmol), anhydrous pyridine (0.0065 ml, 0.082 mmol), CH$_2$Cl$_2$ (5 mL), and (Br$_2$)$_4$-CB[6].10H$_2$O (0.391 g, 0.215 mmol). Bromobenzene 14 was obtained as a pale yellow oil (0.0716 g, 0.459 mmol, 56%).
1.2.14. Formation of \textit{trans}-2-Bromo-cyclohexanol from Cyclohexene with NBS$^{10}$

To a suspension of cyclohexene 15 (0.082 g, 1.0 mmol) and NH$_4$OAc (0.0077 g, 0.10 mmol) in acetone (4 mL), were added NBS (0.20 g, 1.1 mmol) and H$_2$O (1 mL). The mixture was stirred at rt. After completion of the reaction, the mixture was concentrated in vacuum and extracted with EtOAc-H$_2$O (1:1) (3x5 mL). The organic layer was dried over anhydrous MgSO$_4$, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (2% AcOEt in Hexane) to obtain pure \textit{trans}-2-bromo-cyclohexanol (16)$^{10}$ (0.15 g, 0.85 mmol, 85%).

1.2.15. Formation of \textit{trans}-2-Bromo-cyclohexanol from Cyclohexene with Br$_2$-CB[6]

As in 1.2.14, but using cyclohexene 15 (0.082 g, 1.0 mmol), NH$_4$OAc (0.0077 g, 0.10 mmol), (Br$_2$)$_4$-CB[6].10H$_2$O (0.45 g, 0.25 mmol) in H$_2$O (5 mL). The product 16$^{10}$ (0.12 g, 0.70 mmol, 70%) was obtained as a pale yellow oil.

1.2.16. Preparation of \textit{trans}-2-Bromo-cyclopentanol from Cyclopentene with Br$_2$-CB[6]

As in 1.2.15, but using cyclopentene 18 (0.068 g, 1.0 mmol), NH$_4$OAc (0.0077 g, 0.10 mmol), (Br$_2$)$_4$-CB[6].10H$_2$O (0.45 g, 0.25 mmol) in H$_2$O (5 mL). \textit{trans}-Bromocyclopentanol 19$^{10}$ (0.12 g, 0.74 mmol, 74%) was obtained as a pale yellow oil.
1.2.17. Allylic Bromination of Cyclohexene with NBS

Cyclohexene 15 (0.51 mL, 5.0 mmol) was added to a suspension of (PhCO)$_2$ (0.012 g, 0.050 mmol) and NBS (0.18 g, 1.0 mmol) in anhydrous CCl$_4$. The mixture was refluxed for 15 h, filtered, and concentrated on vacuum. The crude product was purified by flash column chromatography (5% AcOEt in hexane) to obtain 3-bromo-cyclohexene (20) (0.089 g, 0.056 mmol, 56%) as a colorless liquid.

1.2.18. Formation of trans-1,2-Dibromocyclohexane from Cyclohexene with Br$_2$-CB[6]

As in 1.2.17, but using cyclohexene 15 (0.51 g, 5.0 mmol), (PhCO)$_2$ (0.012 g, 0.050 mmol), and (Br)$_2$$_4$-CB[6].10H$_2$O (2.27 g, 1.25 mmol) in anhydrous CCl$_4$. trans-1,2-Dibromocyclohexane (17) (0.16 g, 0.65 mmol, 65%) was obtained as a pale yellow oil.

2. References