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A CONVENIENT SYNTHETIC ROUTE TO 1,2,4-TRI AND 1,3-DISUBSTITUTED CUBANES

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Summary: *a convenient synthetic route to 1,2,4-tri and 1,3-disubstituted cubanes based on a selective mono-functionalization of bis-amidocubane* **1** *has been developed.*

In recent years, saturated policyclic "cage" molecules have held a special fascination for organic chemist.[1] Of the many convex "Platonic solids", only one carbocyclic $(CH)_n$ analogue of tetrahedron, the cube, is accessible to synthetic organic chemists as 1,4-dicarbomethoxy derivative in multikilo quantities.

The aesthetic appeal of cubane lies in its symmetry (O_h), in its unusual kinetic stability, and in the unique tridimentional arrangement of substituents. This latter feature has led us to consider the possible existence of therapeutics.

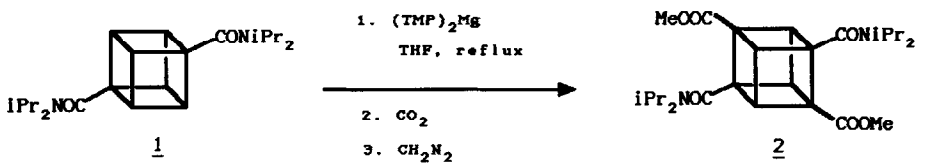
With the aim of preparing cubane derivatives possessing different patterns of substitution, we needed a method for a selective mono-functionalization of **1** that could provide a key intermediate for the preparation of a wide variety of 1,2,4-tri and 1,3-disubstituted cubanes.

Hauser bases and magnesium diamides were recently shown to be efficient ortho-metallating agents towards "activated" aromatics, cyclopropanes and cubanes.[2] In particular, the N,N-diisopropylamido group was used to direct the ortho-metallation of the cubane skeleton.

In fact, the ortho-magnesiation of 1,4-bis-(N,N-diisopropylamido)cubane

1 with excess bis-N-(2,2,6,6-tetramethylpiperidino)magnesium $(TMP)_2Mg$ in refluxing THF, followed by carboxylation and esterification gives dimethyl 1,4-diamide 2,7-diester 2 in better than 80% isolated yield (Scheme 1).[2]

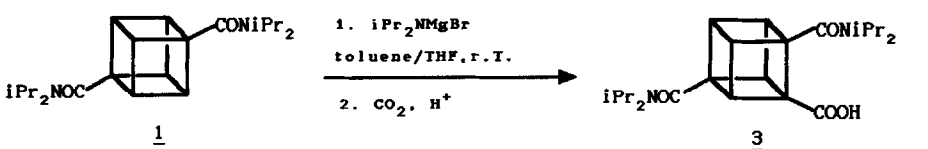
Scheme 1



We now wish to report a simple method of selective mono-functionalization of 1 (Scheme 2) and an example of its further transformation into 1,2,4-tri and 1,3-disubstituted derivatives (Scheme 3).

In our hands the combination of using iPr_2N-Mg-Br as base and toluene/THF mixture as solvent proved to be the most efficient way of performing the mono-functionalization of 1 to provided 3 in better than 70% isolated yield (Scheme 2).[3] Since the carboxylic group can be easily manipulated, compound 3 represents a versatile synthon for the preparation of a variety of cubane derivatives.

Scheme 2

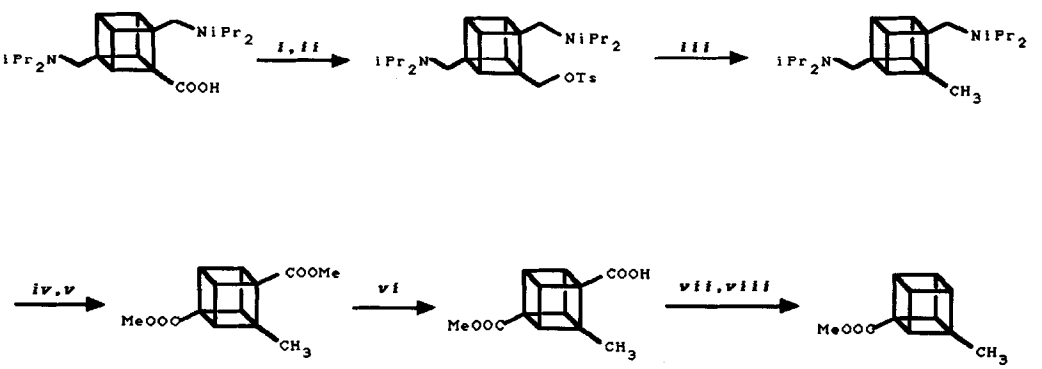


A typical procedure is as follows: To a stirred solution of iPr_2N-Mg-Br (90 mmol) in toluene/THF (150 ml),[4] under nitrogen, 1 (20 mmol, 7.16 g) was added in one amount at room temperature (20-25°C). After the reaction mixture had been stirred at room temperature for 6 hours, it was cooled using a dry ice/acetone bath for 0.5 hour; CO_2 was bubbled through the solution for 1 hour. The cooling bath was removed, the reaction mixture was warmed up at room temperature, quenched with water and neutralized with dilute HCl.

The organic phase was discarded[5] and the aqueuos phase extracted twice with toluene and acidified with diluted HCl to pH 1. The aqueous layer was extracted with dichloromethane and the combined organic phase was washed with water and dried over sodium sulfate. Evaporation of solvent gave **3** (5.80 g, 14.4 mmol, 72% yield).[6]

Scheme 3 illustrates an example of further transformation of **3** into 1,2,4-tri and 1,3-disubstituted cubanes required for our search for biologically active cubane derivatives. Further work is in progress with the aim of providing a simple means of access to unknown cubanes derivatives.

Scheme 3



i) $LiAlH_4$, THF, r.T. 4 h, 90% *ii)* TsCl, Py, 0°C overnight, 70% *iii)* $LiAlH_4$, THF, -20°C, 73% *iv)* $KMnO_4$, aq. NaOH, 0°C then H^+, 90% *v)* CH_2N_2 in Et_2O, 95% *vi)* 1 eq. NaOH in MeOH, 0°C, 85% *vii)* CO_2Cl_2, 98% *viii)* Barton's decarboxylation procedure, 90%.[7]

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References

1) "Strained Organic Compounds" in *Chem.Rev.* **1989**, 5, 973-1215

2) Eaton, P.E.; Lee, C.H.; Xiong, Y. *J.Am.Chem.Soc.* **1990**, *111*, 8016.

3) Although in Reference 1 it is reported that at room temperature using iPr_2N-Mg-Br in THF the reaction can be controlled easily to give monometallation and thus monocarboxylation we were able to obtain such selectivity only at very low conversion of 1.

4) The iPr_2N-Mg-Br solution was obtained by adding a 2M solution of Et-Mg-Br in THF (90 mmol) with stirring under nitrogen to a solution of N,N-diisopropylamine (100 mmol) in toluene (100 ml) while keeping the temperature below 25°C. The solution was then kept overnight at room temperature and then used.

5) Evaporation of the solvent leads to the recovery of unreacted 1 which can be recycled without further purification.

6) ^{1}H-NMR and glc analyses of the crude product after derivatization with diazomethane showed the presence of 2 to an extent of less than 2%. Crystallization from hexane/diethyl ether led to pure 3. ^{1}H-NMR ($CDCl_3$-TMS,200 MHz) δ (ppm): 1.20 (d, 3H, J= 10 Hz),1.22 (d,3H, J= 10Hz), 1.38 (d, 6H, J= 10 Hz), 3.39 (m, 3H), 3.58 (m, 1H), 4.10 (m,2H), 4.28(m,1H), 4.38 (m, 2H); IR (Nujol mull) $\nu_{C=O}$: 1710 and 1630 cm^{-1}.

7) Barton, D.H.R.; Crich, D.; Motherwell, W.B. *J. Chem. Soc. Chem. Commun.* **1983**, 939

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