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An Efficient Triple Allylation of 1,3,5-Triazine by Means of Tin Reagent. Facile Synthesis of syn,syn-2,4,6-Trifunctionalized 1,3,5-Triazacyclohexanes

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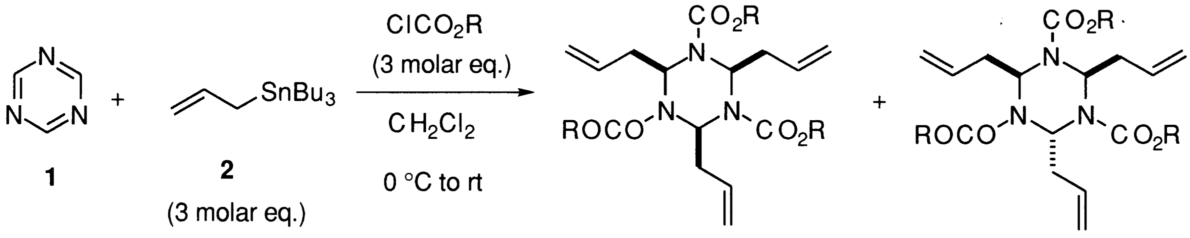
An efficient triple addition of allyl groups to 1,3,5-triazine has bee carried out by means of an allyltin reagent to give 2,4,6-trially-1,3,5-triazacyclohexanes in high yields. Epoxidation and hydroxylation of the syn,syn-stereoisomer afford geometrically interesting syn,syn-trifunctionalized 1,3,5-triazacyclohexane derivatives.

Development of efficient allylation reactions using allylic metal reagents have been one of the key objectives in synthetic organic chemistry.1) We have uncovered that allylic tin reagents react with nitrogen heteroaromatics and cyclic imines activated by a variety of acyl chlorides chemo- and/or regioselectively.2) The important point is that tin reagents do not react either with acyl chlorides or with C=N bonds, but they do react with *N*-acylated iminium ions. In light of the high chemoselectivity, we have anticipated that a polyazaaromatic compound may be polyallylated with stoichiometric amounts of an allyltin reagent in the presence of stoichiometric amounts of an acyl chloride. We report herein that 1,3,5-triazine reacts chemoselectively with 3 equivalents of allyltributyltin in the presence of 3 equivalents of chloroformate esters to give 2,4,6-triallyl-1,3,5-triazacyclohexanes very efficiently.

When 3 equivalents of methyl chloroformate were added to a mixture of 1,3,5-triazine (**1**) and 3 equivalents of allyltributyltin (**2**), a triple addition reaction readily proceeded to give syn,syn- and syn,anti-2,3,4-triallyl-1,3,5-trimethoxycarbonyl-1,3,5-triazacyclohexane (**3a** and **3b**) in a ratio of 20:80 in 87% yield. The stereochemistry of **3a** and **3b** was deduced by ^{1}H and ^{13}C NMR: the NMR spectra of **3a** exhibit higher symmetry than those of **3b**.3,4)

It has been found that the ratio of the stereoisomer is dependent on the kind of chloroformate ester. The results are summarized in the Table 1. When 2,2,2-trichloroethyl chloroformate was used as activating agent, the ratio of syn,syn-:

syn,anti-stereoisomers (**4a** : **4b**) was 40:60. Furthermore, the reaction of **1** with **2** in the presence of phenyl chloroformate gave syn,syn- and syn,anti-stereoisomer (**5a** and **5b**) in a ratio of 42:58 in 92% yield. In a statistical point of view, the percentage of the syn,syn-stereoisomer should be 25%. Thus, sterically demanding chloroformate esters might to increase the ratio of syn,syn-stereoisomer.5)



3a : R = Me
4a : R = CH_2CCl_3
5a : R = Ph

3b : R = Me
4b : R = CH_2CCl_3
5b : R = Ph

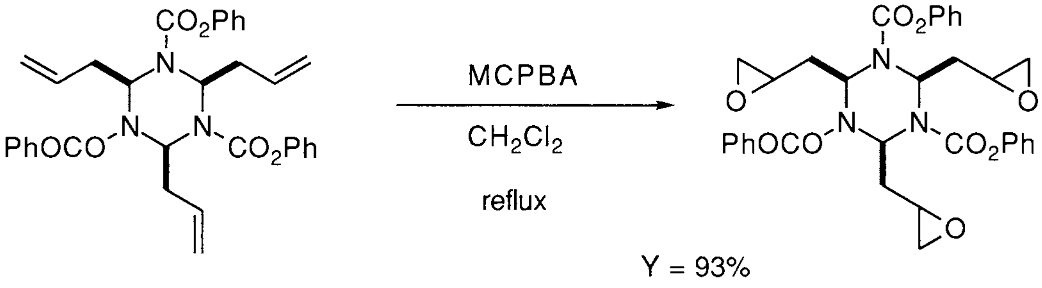
Table 1. Reaction of allyltributyltin (**2**) with 1,3,5-triazine (**1**) activated by chloroformate esters

R	Product	Yield / %[a]	Ratio[b]
Me	**3a**, **3b**	87	**3a**:**3b** = 20:80
CH_2CCl_3	**4a**, **4b**	68	**4a**:**4b** = 40:60
Ph	**5a**, **5b**	92	**5a**:**5b** = 42:58

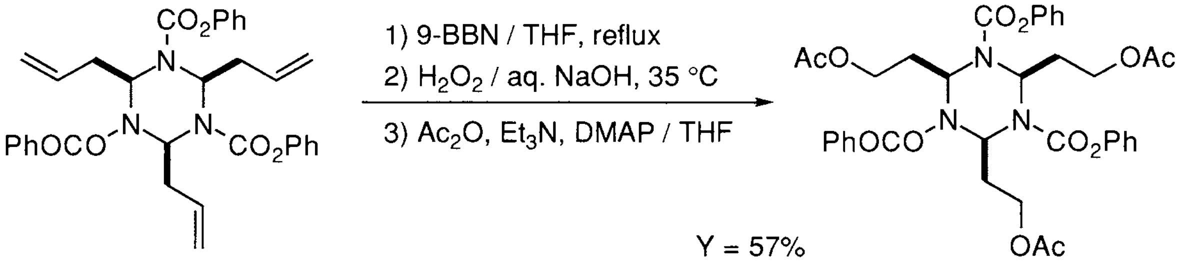
a) Isolated, combined yield. b) Determined by ^1H NMR.

Since syn,syn-2,4,6-triallyl-1,3,5-triazacyclohexane derivatives are geometrically interesting molecules,6) we next examined functionalization of the allyl groups. When **5a** was heated with 6 equivalents of MCPBA in CH_2Cl_2, epoxidation proceeded smoothly to afford syn,syn-2,4,6-tris(2,3-epoxypropyl)-1,3,5-triphenoxycarbonyl-1,3,5-triazacyclohexane (**6**) in 93% yield.7) The triepoxide **6** may be a versatile synthetic intermediate for further manipulations. In addition, **5a** was converted to the corresponding triol via hydroboration. Thus, **5a** was hydroborated with 6 equivalents of 9-BBN in THF at 60 °C. Subsequent oxidation with H_2O_2 in aqueous NaOH at 30—35 °C followed by acetylation gave syn,syn-2,4,6-tris(3-acetoxypropyl)-1,3,5-triphenoxycarbonyl-1,3,5-triazacyclohexane (**7**) in 57% overall yield.8)

In summary, we have found a highly efficient triple allylation of 1,3,5-triazine by means of an allyltin reagent. Further manipulations of a syn,syn-triallylated product afford geometrically interesting syn,syn-2,4,6-trifunctionalized 1,3,5-triazacyclohexane derivatives.



5a **6**



5a **7**

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3) All new compounds gave satisfactory analytical and spectral data.

4) A typical experimental procedure is as follows: To a solution of **1** (81 mg, 1.0 mmol) and **2** (1080 mg, 3.3 mmol) in dry CH_2Cl_2 (5 mL) was added $ClCO_2Ph$ (0.42 mL, 3.0 mmol) under ice-cooling. The solution was stirred at rt overnight and the solvent was evaporated. The residue was chromatographed on silica gel (hexane / CH_2Cl_2 = 10/0 to 0/10) to give **5a** (221 mg, 39%) and **5b** (304 mg, 53%). **5a**: IR (neat) 1722, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.11—7.40 (m, 15H), 6.80 (br t, 3H, J = 8

Hz), 5.92—6.02 (m, 3H), 5.21—5.31 (m, 6H), 3.01 (br t, 3H, *J* = 7 Hz); ^{13}C NMR (CDCl3) δ 152.4 (C), 151.0 (C), 132.9 (CH), 129.4 (CH), 125.8 (CH), 121.5 (CH), 119.0 (CH_2), 62.1 (CH), 42.1 (CH_2). Anal. Found: C, 69.61; H, 5.76%. Calcd for $C_{33}H_{33}N_3O_6$: C, 69.82; H, 5.86%. **5b**: IR (neat) 1722, 1490 cm^{-1}; ^{1}H NMR (CDCl3) δ 7.14—7.44 (m, 15H), 6.45 (br t, 1H, *J* = 7 Hz), 6.23 (br s, 2H), 5.89—6.02 (m, 3H), 5.17—5.38 (m, 6H), 3.32 (br, 2H), 2.68—2.96 (br m, 4H); ^{13}C NMR (CDCl3) δ 153.3 (C), 152.2 (C), 151.9 (C), 150.7 (C), 150.5 (C), 133.2 (CH), 133.0 (CH), 132.0 (CH), 129.6 (CH), 129.5 (CH), 126.1 (CH), 125.9 (CH), 121.5 (CH), 121.4 (CH), 120.4 (CH_2), 118.7 (CH_2), 118.5 (CH_2), 66.0 (CH), 65.6 (CH), 65.4 (CH), 39.7 (CH_2), 39.5 (CH_2). Anal. Found: C, 69.86; H, 5.79%. Calcd for $C_{33}H_{33}N_3O_6$: C, 69.82; H, 5.86%.

5) All substituents of the syn,syn-stereoisomers can adopt equatorial conformation, while those of the syn,anti-stereoisomers can not.

6) They may be potential precursors for novel tridentate coordination compounds.

7) Spectral and analytical data of **6**: mp 82—83 °C; IR (KBr) 1722 cm^{-1}; ^{1}H NMR (CDCl3) δ 7.17—7.42 (m, 15H), 6.97 (br, 3H), 3.19—3.31 (m, 3H), 2.83 (br s,, 3H), 1.95—2.64 (br m, 9H); ^{13}C NMR (CDCl3) δ 152.4 (C), 152,1 (C), 151.8 (C), 151.0 (C), 150.9 (C), 150.7 (C), 129.4 (CH), 126.0 (CH), 125.9 (CH), 121.6 (CH), 121.4 (CH), 60.9 (CH), 60.8 (CH), 49.3 (CH), 49.2 (CH), 49.0 (CH), 49.0 (CH), 46.5 (CH_2), 46.1 (CH_2), 46.0 (CH_2), 40.9 (CH_2). Anal. Found: C, 64.36; H, 5.31%. Calcd for $C_{33}H_{33}N_3O_9$: C, 64.38; H, 5.40%.

8) Spectral and analytical data of **7**: IR (neat) 1733 cm^{-1}; ^{1}H NMR (CDCl3) δ 7.38 (t, 6H, *J* = 7 Hz), 7.17—7.26 (m, 9H), 6.81 (br t, 3H, *J* = 8 Hz), 4.19 (t, 6H, J = 6 Hz), 2.22—2.28 (m, 6H), 2.05 (s, 9H), 1.90—1.95 (m, 6H); ^{13}C NMR (CDCl3) δ 170.9 (C1), 152.5 (C), 150.8 (C), 129.5 (CH), 126.1 (CH), 121.5 (CH), 63.4 (CH_2), 62.3 (CH), 33.9 (CH_2), 25.5 (CH_2), 20.9 (CH_3). Anal. Found: C, 62.43; H, 5.97%. Calcd for $C_{39}H_{45}N_3O_{12}$: C, 62.64; H, 6.06%.

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