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POLYALKYLATION OF 2,2-BIS(HYDROXYMETHYL)-1-ALKANOLS WITH *TERT*-BUTYL BROMOACETATE

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ABSTRACT

A series of 2,2-bis(hydroxymethyl)-1-alkanols was poly-O-alkylated in satisfactory yields with the *tert*-butyl bromoacetate by phase transfer catalysis. The resulting pure polyesters were converted in polyacids in quantitative yields.

The synthesis of tripodal triether acid compounds has been investigated to prepare dendrimers,[1,2] non-macrocyclic receptors for transition metal or lanthanide ions,[3,4,5] or polypodal ligands as phase transfer catalysts.

The O-alkylation of some primary polyols with ethyl diazoacetate has been described,[6] but it gives product mixtures and is not compatible with functional groups such as amino groups. With *tert*-butyl bromoacetate, examples of diol O-alkylations[7–9] are reported in the literature. These O-alkylation procedures applied to primary polyols like the triols **1-5** and the pentaerythritol **6** gave unsatisfactory low yields. Particularly, the classical Williamson synthesis using deprotonation with sodium hydride in

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DMF or DMSO and addition of *tert*-butyl bromoacetate resulted in complex product mixtures, including side products with more *tert*-butyl groups than expected (^{1}H NMR). Their formation is probably due to the presence of excess base, leading to further alkylation of the acidic α-position of the α-oxy-substituted esters present in the products.

A phase transfer catalysis procedure has been described by Nouguier[10] for the etherification of pentaerythritol **6** and trimethylolpropane **1** with alkyl halides. With *tert*-butyl bromoacetate, this method also gave low yields.

In this communication, it is shown that the 2,2-bis(hydroxymethyl)-1-alkanols **1-6** can be conveniently alkylated by *tert*-butyl bromoacetate in acceptable yields under phase transfer catalysis (PTC). The results of our O-alkylation experiments are collected in Table 1 for polyols **1-5**. The reported yields are for isolated products.

Two secondary products, *tert*-butyl fumarate and *tert*-butyl diglycolate, are also obtained in variable yields that depend on the reaction temperature (the fumarate quantities increase greatly if this temperature is

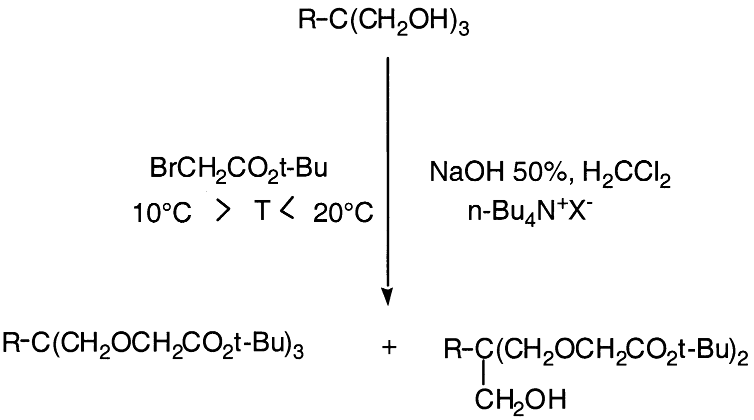


***Table* 1.**

	R	Yield	
1	CH_3	48%	17%
2	C_2H_5	59	36
3	n-$C_{10}H_{23}$	38	23
4	C_6H_5	65	15
5	$N(CH_2Ph)_2$	53	—

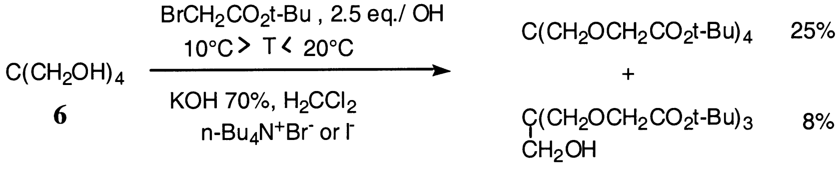
above 20°C), and on whether an excess of *tert*-butyl bromoactetate is used. These two compounds are formed exclusively from *tert*-butyl bromoacetate. The *tert*-butyl fumarate formation results from the acidic methylene group of *tert*-butyl bromoacetate: a self-condensation, followed by an hydrobromation elimination. The nucleophilic substitution of the bromide by the hydroxyl anion, followed by the alcoolate formation explains the expected production of *tert*-butyl diglycolate ether.[11]

The monoethers of polyols **1-5** were never isolated. The absence of formation of monoalkylated products can be rationalized by the fact that the mono(tetra-butylammonio)-triol salts are not transported into the organic phase.[10]

The phase transfer catalyst is usually the *tert*-butyl ammonium bromide, but the iodide or hydrogenosulfate salts give similar results. Conversely, with the tetra-octyl ammonium bromide, regarded as a good transfer reagent[11] for O-alkylation by PTC, the yields of alkylated products are slightly lower.

After optimization, it appeared that the reaction time was an important factor and should be less than 3 h.

The extension of the same experimental procedure to the very hydrophilic primary polyols such as pentaerythritol **6** and tris(hydroxymethyl)-aminomethane **7** (TRIS) lead to O-alkylated products with less that 5% yields. By reacting **6** with saturated solution of potassium hydroxide (70%) instead of sodium hydroxide (50%), two alkylated products were obtained (Scheme 1). *Tert*-Butyl fumarate and *tert*-butyl diglycolate are also isolated in a nearly 60% yield from *tert*-butyl bromoacetate.



Scheme 1.

With these experimental conditions, the tris(hydroxymethyl)aminomethane **7** always gives less than 5% of the tri O-alkylated product. This result may be explained by the fact that the tri(tetra-butylammonium) salt is not conveniently transported into the organic phase.

The new tri-*tert*-butyl esters were obtained from polyols **1-5** and the tetra-*tert*-butyl ester from **6** were easily hydrolyzed in quantitative yields by formic acid.

In conclusion, this study reveals several features necessary to achieve the polyol O-alkylation with *tert*-butyl bromoacetate. Classical Williamson procedures fail with these primary polyols **1-6.** The PTC etherifications afford better results, particularly with more lipophilic polyols. The observed poly O-alkylations and the absence of monoalkylation products agree with Nouguier's results.[10] The secondary reactions of *tert*-butyl bromoacetate should be slower than the polyol O-alkylation rates to prevent the side products being formed in excess.

EXPERIMENTAL

Materials and Instrumentation

NMR spectra were recorded on a Bruker AC 200 spectrometer (^{1}H: 200.13 MHz, ^{13}C: 50.32 MHz) using $CDCl_3$ or D_2O (polyacids) as a solvent. Melting points are uncorrected. All compounds have IR, ^{1}H, ^{13}C NMR spectra and mass spectra consistent with their assigned structures. All IR spectra of *tert*-butyl polyesters show a very strong ν C = O band between 1745 and 1750 cm^{-1}. The polyols **1**, **2**, **6**, and **7** are commercially available. The compounds **3** (12), **4** (12), and **5** (2) were prepared as per the procedures reported in the literature.

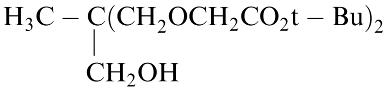
Typical Procedure for Phase Transfer Catalysis

In a chilled sodium hydroxide solution (50%, 6 g, 150 mmol in 6 mL), polyol (5 mmol), H_2CCl_2 (6 mL), and phase transfer catalyst (0.75 mmol) were stirred together, maintaining the temperature between 10° and 20°C. *Tert*-butyl bromoacetate (16 mmol) was added dropwise and stirred for 3 h. The temperature of the reaction mixture was maintained below 20°C. H_2O (10 mL) and pentane (40 mL) were added and stirred for 10 min. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residual oil was purified by chromatography using silica gel (40 g, Merck 60, 0.2 mm, cyclohexane/ethyl acetate gradient from 10:0 to 8:2). The elution order was: *tert*-butyl fumarate, *tert*-butyl diglycolate, tri- or tetra- *tert*-butyl esters, and poly *tert*-butyl esters-alcohol.

$H_3C–C(CH_2OCH_2CO_2t\text{-}Bu)_3$

Transparent viscous oil. **^{1}H**: 1.04 (s, 3H, $C\underline{H}_3C$), 1.47 (s, 27H, $C(C\underline{H}_3)_3$), 3.46 (s, 6H, $CC\underline{H}_2O$), 3.95 (s, 6H, $OC\underline{H}_2CO_2tBu$). **^{13}C**: 17.09

($\underline{C}H_3$-C), 28.10 ($C(\underline{C}H_3)_3$), 40.94 ($CH_3\underline{C}$), 69.46 and 74.34 ($C\underline{C}H_2O\underline{C}H_2CO_2tBu$), 81.26 ($\underline{C}(CH_3)_3$), 169.89 ($\underline{C}O_2tBu$). **MS**: *m*/*z* 463 ($MH^+$). **Anal**. Calc. for $C_{23}H_{42}O_9$: C, 59.7; H, 9.2. Found: C, 59.5; H, 9.1.

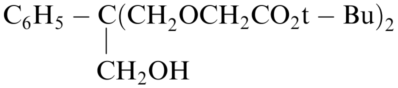


$$H_3C - \underset{\displaystyle CH_2OH}{\overset{}{C}}(CH_2OCH_2CO_2t - Bu)_2$$

Transparent viscous oil. ^{1}**H**: 0.95 (s, 3H, $C\underline{H}_3C$), 1.48 (s, 18H, $C(C\underline{H}_3)_3$), 3.46 (s, 4H, $CC\underline{H}_2O$), 3.54 (d, 2H, J = 6.6 Hz, $C\underline{H}_2OH$), 3.71 (t, 1H, J = 6.6 Hz, $CH_2O\underline{H}$), 3.95 (s, 4H, $OC\underline{H}_2CO_2tBu$). ^{13}**C**: 17.09 ($\underline{C}H_3$-C), 28.10 ($C(\underline{C}H_3)_3$), 40.94 ($CH_3\underline{C}$), 68.45 ($\underline{C}H_2OH$), 74.31 and 69.43 ($C\underline{C}H_2O\underline{C}H_2CO_2tBu$), 81.26 ($\underline{C}(CH_3)_3$), 169.88 ($\underline{C}O_2tBu$). **MS**: *m*/*z* 349 ($MH^+$). **Anal**. Calc. for $C_{17}H_{32}O_7$: C, 58.6; H, 9.3. Found: C, 58.5; H, 9.5.

C_6H_5—$C(CH_2OCH_2CO_2t\text{-}Bu)_3$

M.p. 60°–62°C ^{1}**H**: 1.47 (s, 27H, $C(C\underline{H}_3)_3$), 3.93 (s, 6H, $CC\underline{H}_2O$), 3.96 (s, 6H, $OC\underline{H}_2CO_2tBu$), 7.3–7.6 (m, 5H, $C_6\underline{H}_5$). ^{13}C: 28.13 ($C(\underline{C}H_3)_3$), 48.40 ($C_6H_5\underline{C}$), 69.71 and 73.87 ($C\underline{C}H_2O\underline{C}H_2CO_2tBu$), 81.33 ($\underline{C}(CH_3)_3$), 126.62, 127.40, 128.14, 140.98 ($\underline{C}_6H_5$), 169.77 ($\underline{C}O_2tBu$). **MS**: *m*/*z* 542 ($M+NH_4^+$). **Anal**. calc. for $C_{28}H_{44}O_9$: C, 64.1; H, 8.5. Found: C, 63.9; H, 8.6.



$$C_6H_5 - \underset{\displaystyle CH_2OH}{\overset{}{C}}(CH_2OCH_2CO_2t - Bu)_2$$

Transparent viscous oil. ^{1}**H**: 1.47 (s, 18H, $C(C\underline{H}_3)_3$), 3.85 (d, 2H, $C\underline{H}_2OH$), 3.96 (s, 8H, $C\underline{H}_2OC\underline{H}_2$), 4.10 (t, 1H, $CH_2O\underline{H}$), 7.3–7.6 (m, 5H, $C_6\underline{H}_5$). ^{13}**C**: 27.98 ($C(\underline{C}H_3)_3$), 48.63 ($C_6H_5\underline{C}$), 65.69, 68.70 and 74.10 ($C\underline{C}H_2O\underline{C}H_2CO_2tBu$ and $\underline{C}H_2OH$), 81.89 ($\underline{C}(CH_3)_3$), 126.57, 126.93, 128.20, 140.77 ($\underline{C}_6H_5$), 170.27 ($\underline{C}O_2tBu$). **MS**: *m*/*z* 411 (MH^+). **Anal**. calc. for $C_{22}H_{34}O_7$: C, 64.4; H, 8.3. Found: C, 64.0; H, 8.7.

$(PhH_2C)_2N$—$C(CH_2OCH_2CO_2t\text{-}Bu)_3$

Transparent viscous oil. ^{1}**H**: 1.46 (s, 27H, $C(C\underline{H}_3)_3$), 3.75 (s, 6H, $CC\underline{H}_2O$), 3.85 (s, 6H, $OC\underline{H}_2CO_2tBu$), 4.05 (s, 4H, $C\underline{H}_2Ph$), 7.05–7.19 (m, 10H, $C_6\underline{H}_5$). ^{13}C: 28.10 ($C(\underline{C}H_3)_3$), 54.72 ($N\underline{C}CH_2O$), 64.39 ($N\underline{C}H_2Ph$), 69.43 and 72.24 ($C\underline{C}H_2O\underline{C}H_2CO_2tBu$), 81.20 ($\underline{C}(CH_3)_3$), 125.99, 127.55, 128.41, 142.34 ($\underline{C}_6H_5$), 169.65 ($\underline{C}O_2tBu$). **MS**: *m*/*z* 644

(MH^+). **Anal**. calc. for $C_{36}H_{53}O_9$: C, 57.72; H, 8.84. Found: C, 57.62; H, 8.86.

$C(CH_2OCH_2CO_2t\text{-}Bu)_4$

M.p. 93°–94°C. **^{1}H**: 1.46 (s, 36H, $C(C\underline{H}_3)_3$), 3.63 (s, 8H, $CC\underline{H}_2O$), 3.96 (s, 8H, $OC\underline{H}_2CO_2tBu$). ^{13}C: 28.01 ($C(\underline{C}H_3)_3$, 45.20 ($\underline{C}(CH_2)_4$), 69.42 and 70.75 ($C\underline{C}H_2O\underline{C}H_2CO_2tBu$), 81.08 ($\underline{C}(CH_3)_3$, 169.70 ($\underline{C}O_2tBu$). **MS**: *m/z* 593 (MH^+). **Anal**. calc. for $C_{29}H_{52}O_{10}$: C, 58.78; H, 8.84. Found: C, 58.90; H, 8.72.

$$\underset{\displaystyle CH_2OH}{\underset{|}{C}}(CH_2OCH_2CO_2t-Bu)_2$$

Transparent very viscous oil. **^{1}H**: 1.47 (s, 27H, $C(C\underline{H}_3)_3$), 2.35 (s, 1H, $CH_2O\underline{H}$), 3.59 (s, 6H, $CC\underline{H}_2O$), 3.71 (s, 2H, $C\underline{H}_2OH$), 3.95 (s, 6H, $OC\underline{H}_2CO_2tBu$). **^{13}C**: 28.04 ($C(\underline{C}H_3)_3$), 45.00 ($\underline{C}(CH_2)_4$), 63.00 ($\underline{C}H_2OH$), 68.95 and 71.23 ($C\underline{C}H_2O\underline{C}H_2CO_2tBu$), 81.64 ($\underline{C}(CH_3)_3$), 170.00 ($\underline{C}O_2tBu$). **MS**: *m/z* 479 (MH^+). **Anal**. calc. for $C_{23}H_{42}O_{10}$: C, 57.72; H, 8.84. Found: C, 57.62; H, 8.86.

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