Organic Process Research & Development **2001**, *5*, 54–60

3,4,5-Tri-dodecyloxybenzoic Acid: Optimisation and Scale-Up of the Synthesis

M. C. Hersmis,‡ A. J. H. Spiering, R. J. M. Waterval, J. Meuldijk, J. A. J. M. Vekemans, and L. A. Hulshof*

Eindhoven University of Technology, Laboratory of Macromolecular and Organic Chemistry and Process Development Group, Department of Chemical Engineering and Chemistry, P.O. Box 513, 5600 MB Eindhoven, The Netherlands

Abstract:

The synthesis of tris-*O*-dodecyl-gallic acid (3,4,5-tri-dodecyloxybenzoic acid)—a versatile building block for organic liquid crystalline materials—has been selected for fine chemical scale-up. A large-scale procedure of the alkylation of methyl gallate was optimised with experimental design techniques. Apart from the solvent effect, also the temperature, phase-transfer catalyst, stirring speed, and amount of base were found to be most significant for the reaction rate. Reaction calorimetry revealed no excessive exothermic reaction steps in the process. Reaction kinetics on the alkylation reaction was studied as a function of particle size distribution of the base, potassium carbonate, and formation of carbon dioxide. Combination of all experimental results has debouched into a master recipe for kilogram-scale synthesis in a 10 dm^3 fully automated (semi)batchwise operated reactor.

Introduction

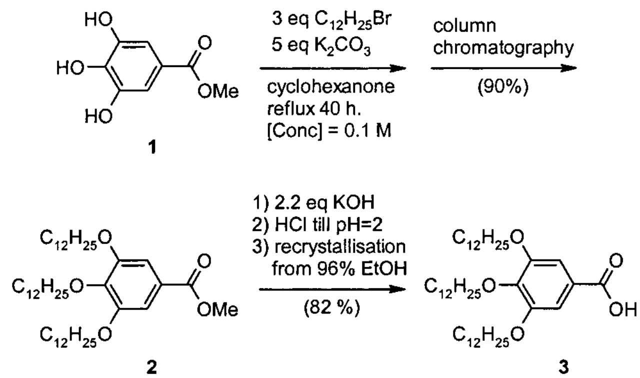
Process research and development for the production of fine chemicals asks for a completely different approach than that for bulk chemicals. Bulk chemicals are produced in large-scale continuous processes, based on detailed, quantitative insights into the chemical and physical aspects of the process and on rigorous process development for one specific product.

In contrast, fine chemicals are usually produced in multipurpose (semi)batchwise operated equipment. New fine chemicals ask for a short time to market and have a relatively short lifetime in the market as compared to that for bulk chemicals. This makes batch-process design quite challenging due to lack of design tools and generic methodologies when compared to continuous processing.

As part of our program to define design tools and a methodology for fine chemical scale-up, tris-*O*-dodecyl-gallic acid (3,4,5-tri-dodecyloxybenzoic acid) was selected as target. Tris-*O*-dodecyl-gallic acid (TDGA) is a versatile building block for the flexible part of discotic liquid crystalline materials.[1−4] Its versatility and broad scope are reflected in diverse applications such as helical tobacco mosaic virus models,[5] intra- and intermolecularly hydrogen-bonded supramolecular polymers,[6] and C_3-symmetrical super helices.[3]

An extensive study was initiated to design the optimal parameters affording a robust process to produce TDGA on a kilogram scale in a 10 dm^3 fully automated (semi)batchwise operated reactor.[7] The newly developed process (master recipe) should be: (1) selective (affording highly pure material in high yield), (2) rapid (high conversion rates), (3) cheap, (4) safe, and (5) environmentally acceptable.

Scheme 1



Optimisation Studies

The described tri-alkylation[3] of methyl 3,4,5-trihydroxybenzoate or methyl gallate (**1**) with 1-bromododecane, depicted in Scheme 1 uses 5 mol equiv of potassium carbonate in cyclohexanone as solvent at a 0.1 M concentration of **1**. The reaction times are approximately 40 h, and the resulting products are purified by column chromatography.[3]

The conversion rate, throughput, and purification as reported by Palmans et al.[3] are not attractive for large-scale

* Author for correspondence: E-mail: L.A.Hulshof@tue.nl.
‡ E-mail: mchersmis@yahoo.com.

(1) Discovered in the nineteenth century by Lehman and Reinitzer[2], liquid crystals constitute a class of molecules sharing mobility and orientational order. Molecular anisotropy or a dichotomy of the structure may provide this ordering. The dichotomy relates to different structural properties (e.g. rigid and flexible)[3] or different chemical properties (e.g. hydrophobic or hydrophilic).[4] Liquid crystalline materials consist of two domains: the rigid part of the molecule, tending to aggregate into large stacks, and the flexible part, which can be derived from TDGA. Liquid crystals exhibit both fluid and solid properties over a certain temperature range. Liquid crystal display (LCD) technology has found new applications in a diverse range of consumer goods, therefore the global demand for new applications of LCD technology is increasing.

(2) (a) Reinitzer, F. *Monath. Chem.* **1888**, *9*, 421. (b) Collins, P. J. *Liquid Crystals*, IOP publishing Ltd, Princeton University Press: New Jersey, **1990**, 24−34.

(3) Palmans, A. R. A.; Vekemans, J. A. J. M.; Fischer, H.; Hikmet, R. A.; Meijer, E. W. *Chem. Eur. J.* **1997**, *3*, 300.

(4) Schenning, A. P. H. J.; Elissen-Román, C.; Weener, J.-W.; Baars, M. W. P. L.; van der Gaast, S. J.; Meijer, E. W. *J. Am. Chem. Soc*. **1998**, *120*, 8199.

(5) Percec, V.; Heck, J.; Lee, M.; Ungar, G.; Alvarez-Castillo, A. *J. Mater. Chem*. **1992**, *2*, 1033.

(6) Sijbesma, R. P.; Beijer, F. H.; Brunsveld, L.; Folmer, B. J. B.; Hirschberg, K.; Lange, R. F. M.; Lowe, J. K. L.; Meijer, E. W. *Science* **1997**, *278*, 1601.

(7) The description of this reactor has been published: Soldaat, A. *Chemisch2Weekblad.* **1999**, *8*, 18.

10.1021/op000066e CCC: $20.00

Published on Web 12/06/2000

***Table 1.* Results prior to factorial design**[a]

exp	solvent	catalyst	99% conversion (h)
1	cyclohexanone	−	5
2	MIBK	−	>48
3	MEK	−	>48
4	MIBK	TBAI[b]	2
5	MEK	TBAI	4
6	MIBK	TBAB[c]	3[d]
7	MIBK	Aliquat 336[e]	1.5

[a] All experiments were performed under reflux conditions with the same batches of **1**, dodecyl bromide, and base. [b] Tetrabutylammonium iodide. [c] Tetrabutylammonium bromide. [d] Poor agitation. [e] Methyltrioctylammonium chloride.

synthesis. Therefore, the reaction was studied on lab-scale with respect to the five criteria mentioned above. Initially, other solvents than those described in the literature,[8] that is, acetone, DMF, and cyclohexanone, were investigated. Apart from aldol-condensation sensitive acetone and toxic DMF, other polar aprotic solvents were studied with special emphasis on the reduction of reaction time. Ketones with increasing boiling points, such as methyl ethyl ketone, methyl isobutyl ketone, and cyclohexanone were selected. A higher reaction rate was expected, provided that the solubility of the reactants and intermediates remains sufficiently high. To further accelerate the alkylation of **1**, the influence of a phase-transfer catalyst (PTC) on the conversion rate was studied.

A set of experiments was designed to screen the solvent and phase-transfer effects rapidly. The experiments, collected in Table 1, were all performed under reflux conditions with 10 mol equiv of potassium carbonate and 10 mol % of PTC, based on the amount of methyl gallate. The reaction was monitored by thin-layer chromatography and ^{1}H NMR. A dramatic effect of the phase-transfer catalyst on the conversion rate was observed in this preliminary study as displayed in Table 1.

The first three entries show that the alkylation is only approximately 10 times faster in cyclohexanone at 155 °C than either in refluxing methyl isobutyl (MIBK) or refluxing methyl ethyl ketone.[9] The data in Table 1 point out that cyclohexanone is a poor solvent for the alkylation of **1**, probably due to the poor solubility of either base or (mono-alkylated) intermediate salts of **1** and the limited polarity. However, entries 4−7 clearly show that phase-transfer catalysis is beneficial. Although Aliquat 336 was the most active PTC—2 times as active as TBAI and 3 times as active as TBAB—the latter was selected as PTC. TBAB is easily available in large quantities and lower-priced per mol than TBAI, and above all, TBAB is more easily removed in downstream-processing than Aliquat 336, which was difficult to separate from compound **2**, according to ^{1}H NMR analysis.[10]

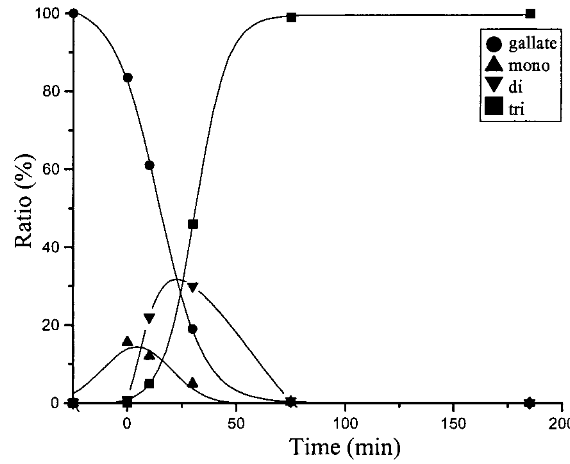
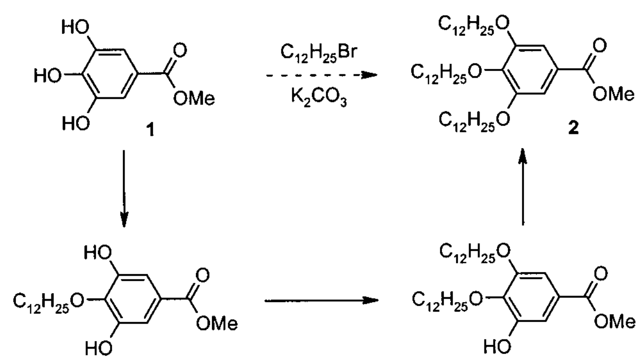


***Figure 1.* Course of three consecutive alkylations of methyl gallate versus time. Reaction conditions: 0.4 M methyl gallate, 6.1 mol eq K_2CO_3, 0.05 mol eq TBAB and 3.2 mol eq 1-bromododecane in MIBK were heated to reflux (t = 0 min.) and maintained at T = 115 °C for 3 h. The moment at which reflux temperature is reached is t = 0.**

Scheme 2



The combination of MIBK with TBAB was chosen as the basis for experimental design. Although Aliquat 366 appeared to be more difficult to remove in the work-up, it was included in the experimental design to study phase-transfer catalytic effects.

The pathway followed by the three consecutive alkylations was studied with ^{1}H NMR spectroscopy. The first *O*-alkylation of **1** did almost exclusively occur at the para position. As a consequence, only asymmetric bis-alkylated methyl gallate was observed, see Scheme 2. An example of the progress of alkylation with time is displayed in Figure 1. The reaction is started at room temperature, and the reaction mixture is heated to reflux. Only mono-alkylation occurs at lower temperatures. The subsequent reactions start upon reaching reflux temperature. Tri-alkylation was completed after 2.5 hours.[11]

Fractional Factorial Design

On the basis of the exploratory results collected in Table 1, the experimental design was set up for the alkylation

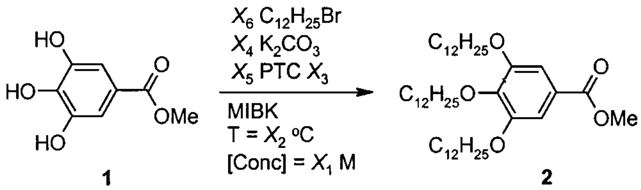
(8) (a) Allen, C. F. H.; Gates, J. W. *Organic Syntheses* **1952**, *3*, 140. (b) Malthête, J.; Tinh, N. H.; Levelut, A. M. *J. Chem. Soc., Chem. Commun*. **1986**, 1548. (c) Johansson, G.; Percec, V.; Ungar, G.; Abramic, D. *J. Chem. Soc.; Perkin Trans. 1.* **1994**, 447.

(9) Since the temperature difference is more than 40 °C, one would expect a larger difference in reaction rate. Based on an activation energy of approximately 90 kJ/mol per mol 1-bromododecane in a temperature range of 0−100 °C a considerably shorter reaction time was expected in cyclohexanone. See also Morrison, R. T.; Boyd, R. N. *Organic Chemistry*, Allyn and Bacon, Inc., Boston, **1987**, 55−58.

(10) To enhance reactivity and catalyst separation see (a) Halpern, M. E.; Grinstein, R. *Spec. Publ. −R. Soc. Chem.* **1999**, *236*, 30. (b) Halpern, M. E.; Grinstein, R. *Spec. Chem.* **1999**, *19*, 204. (c) Halpern, M. E. *ACS Symp. Ser*. **1997**, *659*, 97.

(11) The reaction constants for each of the three consecutive alkylations are not yet determined in view of the complexity of the system.

Table 2. **Variables and minimum and maximum levels used in the factorial design[a]**



X_i	variable	(−)	0	(+)
X_1	conc methyl gallate (mol/L)	0.2	0.3	0.4
X_2	temperature (°C)	95	105	115
X_3	type of PTC[b]	TBAB	0.5/ 0.5[c]	Aliquat 336
X_4	amount of K_2CO_3 (mol equiv)	4.0	6.0	8.0
X_5	amout of PTC (mol equiv)	0.05	0.075	0.10
X_6	amount of $C_{12}H_{25}Br$ (mol equiv)	3.1	3.2	3.3
X_7	stirring speed (rpm)[d]	0	300	600

[a] All experiments were performed with the same batches of chemicals. [b] Phase-transfer catalyst: tetrabutylammonium bromide or methyltrioctylammonium chloride. [c] Mixture of TBAB and Aliquat 336 (mol equiv) [d] Magnetic stirrer equipped with 20 mm stirrer bar.

Table 3. **Fractional factorial design: experimental matrix and results**

	variables							response yield of **2** (%)	
exp	X_1	X_2	X_3	X_4	X_5	X_6	X_7	1.5 h	3 h
1	−	−	−	+	+	+	−	15	30
2	+	−	−	−	−	+	+	17	37
3	−	+	−	−	+	−	+	93	100
4	+	+	−	+	−	−	−	98	99
5	−	−	+	+	−	−	+	38	57
6	+	−	+	−	+	−	−	13	29
7	−	+	+	−	−	+	−	30	57
8	+	+	+	+	+	+	+	99	99
9	−	−	−	−	−	−	−	7	10
10	+	−	−	+	+	−	+	60	91
11	−	+	−	+	−	+	+	96	100
12	+	+	−	−	+	+	−	54	77
13	−	−	+	−	+	+	+	31	53
14	+	−	+	+	−	+	−	22	24
15	−	+	+	+	+	−	−	93	100
16	+	+	+	−	−	−	+	68	88
17	0	0	0	0	0	0	0	63	86
18	0	0	0	0	0	0	0	71	86
19	0	0	0	0	0	0	0	62	82

reactions of **1**. The influence of seven critical process parameters was studied with 16 experiments, a fold-over, and three centre point experiments,[12] see Table 2.

The conversion and selectivity of each experiment were determined by ^1H NMR analysis at 1.5 and 3 h time intervals, enabling a seven-factor set up with two responses, in which the reaction time is used to indicate the time elapsed when the response of product yield is measured. The experiments have been performed in a random order, and the experimental matrix and responses are depicted in Table 3.[13] The selection of the levels for the different factors has been carried out

(12) Box, G. E. P.; Draper, N. R. *Empirical model-building and response surfaces*, John Wiley & Sons: New York, 1987.

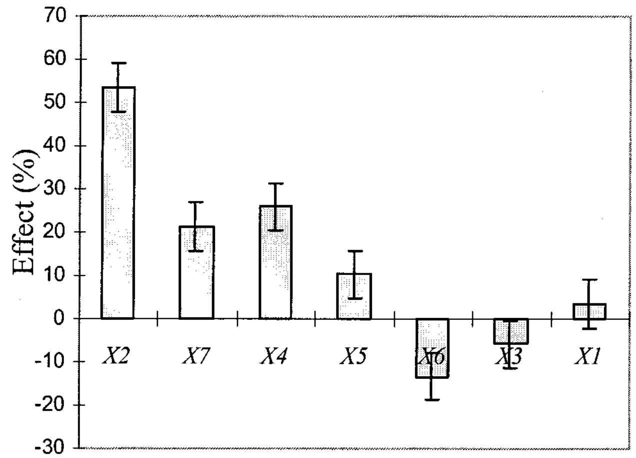


Figure 2. **Results of fractional factorial design after 1.5 h.**

Table 4. **Results factorial design: estimated effects for the experimental variables[a]**

		effect (%)[b]			
X_i	variable	1.5 h	std error	3 h	std error
X_2	temperature	53.5	5.5	48.6	6.3
X_7	stirring speed	21.3	5.5	24.9	6.3
X_4	amount of K_2CO_3	26.0	5.5	18.6	6.3
X_5	amout of PTC	10.3	5.5	13.4	6.3
X_6	amount of $C_{12}H_{25}Br$	−13.3	5.5	-12.1	6.3
X_3	type of PTC	−5.8	5.5	-4.6	6.3
X_1	conc methyl gallate	3.5	5.5	4.6	6.3
	mean value β_0	54.2	2.5	68.7	2.9
	R^2	0.93		0.89	
	Q^2	0.79		0.72	
	RSD	11.0		12.3	

[a] Number of experiments = 16 (excluding 3 centre points). [b] Estimated standard error of the regression coefficient (scaled and centered).

considering previous experiments and the five constraints mentioned in the Introduction.

The results are depicted in Figure 2, and the statistical analysis and significant influences of this factorial design—using the Modde program[14]—are shown in Table 4. The effect of each variable X_i has been calculated using a polynomial function of the seven experimental variables.

The process parameters in Table 4 are ranked according to the estimated and calculated effects. Temperature, stirring speed, and the amount of base were found to be the most important parameters. The concentration of methyl gallate and the type of catalyst are less important parameters. Conclusions could be drawn with respect to the relevance of the parameters. Moreover, due to the fold-over approach, all effects are free from confoundings of first-generation interactions.[15]

A high concentration of methyl gallate would result in more space-time-yield, and the TBAB phase-transfer catalyst can be separated from the product more easily than Aliquat 336 as described above.

(13) The experimental design was generated according to the lines for a fold-over design indicated by R. Carlson, Design and Optimization in Organic Reactions, Elsevier: Amsterdam, 1990, 141−149.

(14) Modde 4.0, Umetri AB, Umeå, Sweden.

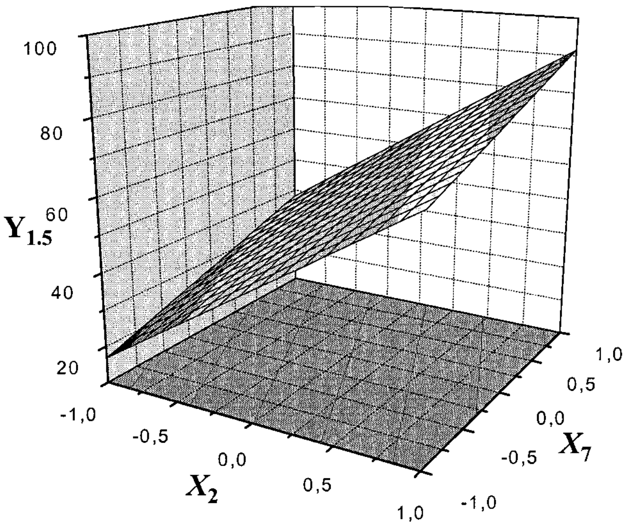


Figure 3. **The response surfaces X_2 (temperature from 95 to 115 °C) vs X_7 (stirring speed from 0 to 600 rpm.) for $Y_{1.5}$ (1). Other variables $X_i = 0$.**

Table 4 also provides information on the optimal reaction conditions. Operating at higher temperatures, stirring at maximal speed, using a large amount of base and catalyst, and working with a small excess of 1-bromododecane should result in a high production rate of **2**. The regression analysis of this factorial design resulted into two models that would fit the experimental data as given in the following equations:[15]

$$Y_{1.5} = 54.2 + 26.8X_1 + 1.8X_2 - 6.6X_3 + 10.6X_4 + 13.0X_5 + 5.1X_6 - 2.9X_7 \quad (1)$$

$$Y_3 = 68.7 + 24.3X_1 + 2.3X_2 - 6.1X_3 + 12.4X_4 + 9.3X_5 + 6.7X_6 - 2.3X_7 \quad (2)$$

wherein:

$Y_{1.5}$, Y_3 = predicted space-time-yield at 1.5 and 3 h, respectively

X_i = variables described in Tables 1 and 4

See Figure 3 for an example of the response surfaces of variables X_2 and X_7. On the basis of the results described in the parts Optimisation Studies and Fractional Factorial Design, three additional experiments were carried out to verify the model eqs 1 and 2 and to fine-tune the reaction conditions. The experimental conditions of these three experiments are presented in Tables 5 and 6.

The experimental conditions in Tables 5 and 6 were the desired ones according to the model eq 1 and in view of further scale-up (heat effects and productivity), leading to 1.5 h reaction time for complete alkylation. A synthesis was performed, and the reaction time turned out to be 1 h as was predicted by the model eq 1. This result confirmed that the required reaction conditions were found. However, the amounts of base and catalyst used, 8 and 0.10 mol equiv per mol **1**, respectively, were rather high. Particularly, a large amount of base is unfavourable for scale-up. Experiment B was set up to investigate whether smaller amounts of base and catalyst, 4 and 0.05 equiv, respectively, could be used without indulging too low reaction rates. The time needed for complete conversion in this experiment was 6 h. The reaction rate dropped dramatically, so a final experiment C with 6 equiv of base and 0.05 equiv of catalyst was carried out. The alkylation proceeded to completion within 1.5 h, and the crude yield based on **1** was nearly quantitative, that is, 99% before purification.

The methyl 3,4,5-tridodecyloxy-benzoate (**2**) was saponified with either sodium or potassium hydroxide in boiling ethanol within 2 h, acidification with hydrochloric acid, followed by cooling gave an off-white lumpy crystalline material, TDGA (**3**) in good yield (86−90%).

Table 5. **Experiments based on the results of the factorial design**

variable	exp A	exp B	exp C
temperature (°C)	115	115	115
stirring speed (rpm)[a]	600	600	600
amount of K_2CO_3 (mol equiv)	8	4	6
amout of PTC (mol equiv)	0.10	0.05	0.05
amount of $C_{12}H_{25}Br$ (mol equiv)	3.1	3.1	3.1
type of PTC	TBAB	TBAB	TBAB
concd methyl gallate (mol/L)	0.4	0.4	0.4
reaction time (h)	1	6	1.5

[a] Magnetic stirrer equipped with 20 mm stirrer bar.

Table 6. **Predicted and obtained results for the optimising experiments**

	response			
	yield predicted (%)		yield observed (%)	
exp[a]	1.5 h	3 h	1.5 h	3 h
exp A	100[b]	100[b]	100[c]	100[c]
exp B	85	100	73	89
exp C	98	100	100[d]	100[d]

[a] Variables in Table 5. [b] Actual prediction was above 100%. [c] Reaction was completed within 1 h. [d] Reaction was completed within 1.5 h.

Thermochemical Properties

The selected reaction conditions for the synthesis of TDGA on lab-scale were determined as described above. A 100 g scale experiment was carried out applying these reaction conditions in a 1 dm^3 reactor, and surprisingly the reaction rate was much lower than in the smaller-scale experiment. Only 25% trialkylated **2** was formed, in 5 h reaction time. On the 1 dm^3 (100 g) scale the same batches of starting materials were used as in the optimisation studies except for the potassium carbonate. Down-scaling to the initial lab-scale with identical batches of starting materials gave the same poor results. Therefore, it was concluded that the quality of K_2CO_3 was the only different factor between these experiments and the optimisation studies. Mass transfer of potassium carbonate turned out to be the most critical factor for the reaction rate. Grinding the base before use gave

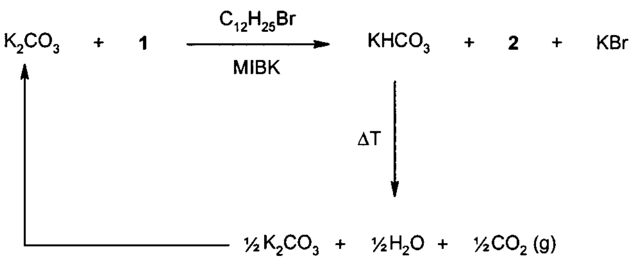
(15) Supplementary information on the statistics is available. Modeling including an interaction term of X_2 X_7 gives some less of fit for the Y 3.0 response as well as a model excluding X_1 and X_3. The best fit was obtained when X_2 was included as a quadratic term (R^2 = 0.94, Q^2 = 0.85 for both responses).

Table 7. **RC1 results: heat of reaction and adiabatic temperature rise**

$$\Delta T_{adia} = \frac{-\Delta H_r \cdot Conc}{C_p}$$

concentration = 0.26 mol/kg, C_p = 2 kJ/kg·K	ΔH_r (kJ/mol)	ΔT_{adia} (K)
trialkylation	−216.6	28
CO_2 formation	38.4	−5
solvatation NaOH	−98.4	13
neutralization HCl	−92.1	12

Scheme 3



the same satisfactory results as before, that is, complete conversion within 2 h, on both 10 and 100 g scale. A particle size study before and after grinding demonstrated that an average particle size of approximately 125 μm or smaller is needed for complete reaction to TDGA within 1.5 h.

Both the tri-alkylation and the saponification/acidification steps are exothermic reactions. To enable further scale-up of the synthesis of TDGA, insight into the heats of reaction and an estimation of the adiabatic temperature rise are required. The thermochemical data for the different reactions was determined with reactor calorimetry. Instead of performing the reaction under reflux conditions, the alkylation was studied at 110 °C to improve the accuracy of the RC1 measurements. The results of the alkylation reaction and saponification/acidification are listed in Table 7.

Although the tri-alkylation step has a reasonably high heat of reaction ($\Delta H_r = -216.6$ kJ/mol per mol methyl gallate), the corresponding adiabatic temperature rise of approximately 30 °C is not problematic during scale-up. The first alkylation step is rather slow at a relatively low concentration since both methyl gallate and K_2CO_3 must solubilise from their solid state.

The heat of dissolution of the solid NaOH in ethanol in the second step can be used to heat the reaction mixture. The saponification is performed at 78 °C under reflux conditions. The subsequent neutralisation can be controlled without difficulties by dosing the hydrochloric acid solution. It was concluded that these three exothermic reaction steps could be managed safely on larger scale.

The reaction calorimetry experiments also showed an endothermic effect after completion of the tri-alkylation, due to gas formation. The released gas was unambiguously identified as carbon dioxide (see Scheme 3). CO_2 formation in time was studied by volumetric techniques. It was relatively constant in time and temperature dependence.[16]

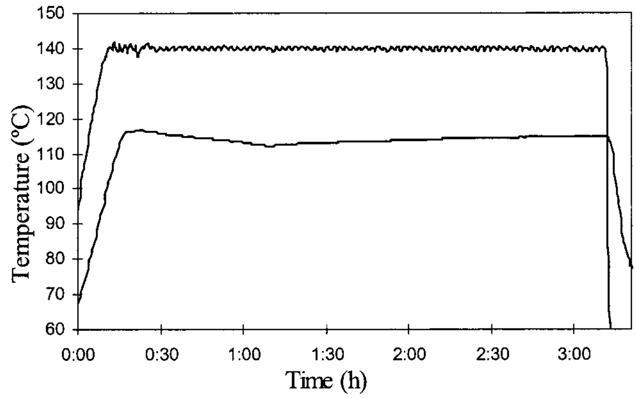


Figure 4. **The temperature profile during the alkylation reaction. Reaction conditions: 0.4 M methyl gallate, 6.1 mol eq K_2CO_3, 0.05 mol eq TBAB and 3.2 mol eq 1-bromododecane in MIBK were heated to reflux and reflux was maintained for 3 h.**

Disproportionation of $KHCO_3$ yields water besides carbon dioxide. This water forms an azeotrope with MIBK,[17] which is clearly illustrated in Figure 4. The reaction started at 115 °C; during the reaction the boiling point of the azeotrope dropped to 112 °C.

Finally, it was concluded that neither release of CO_2 nor the azeotrope formation was significant with respect to the tri-alkylation rate, yield, and scale-up.

One Kilogram Scale

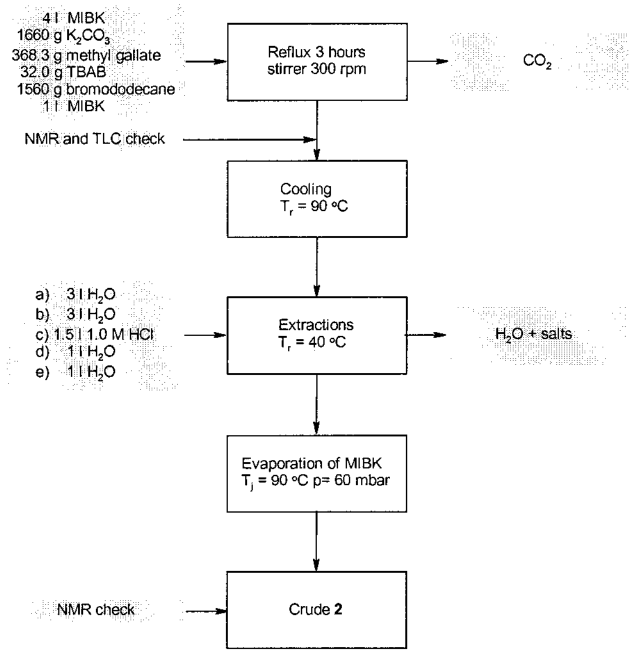
The insights and results described above were translated into a master recipe for a 1 kg product-scale. The starting materials (methyl gallate, K_2CO_3, TBAB, MIBK, and 1-bromododecane) were added to a fully automated 10 dm^3 reactor. The reaction was monitored by ^{1}H NMR, temperature, heat flow, stirring speed, and energy dissipation due to stirring. The alkylation was complete within 2 h. Extraction and solvent evaporation yielded a brown oil, which was saponified with potassium hydroxide in ethanol within 2 h. Neutralisation and cooling to 45 °C afforded an off-white lumpy precipitate, TDGA (**3**). Unfortunately, crude TDGA contained salts, and a purification step was needed. The product was dissolved in dichloromethane, and the insoluble salts were filtered off. Evaporation of the filtrate resulted in pure and white TDGA in 92% yield based on **1** and 99% purity.

The insoluble salts in the residue were identified as mainly consisting of potassium chloride. KCl has a poor solubility in 92% ethanol, that has been used to wash the product during filtration. A few small-scale experiments were carried out to investigate the saponification with lithium hydroxide. Although the reaction times for complete hydrolysis varied from 3 to 4 h, no insoluble salts were formed. LiCl is very soluble in 92% ethanol and hence did not accumulate in the

(16) The release of CO_2 was very small in a temperature range from 25 to 80 °C and increased to 2.0 dm^3/h at 110 °C and atmospheric pressure on 100 g scale. The total amount of CO_2 evolved during the alkylation was 10−15 mol % of the $KHCO_3$ formed in the alkylation. This amount appeared to be constant in time. CO_2 is presumably formed by disproportionation of $KHCO_3$ as depicted in Scheme 3.

(17) Horsley, L. H. *Azeotropic data*, American Chemical Society: Washington, D. C., **1952**; Azeotrope MIBK/H_2O, Wt. % H_2O = 24.3.

Scheme 4. **Block diagram of master recipe for the alkylation of methyl gallate**



product. The TDGA obtained was 99% pure, a small impurity was tentatively identified as 4,4′,5,5′,6,6′-hexakis-(dodecyloxy)-biphenyl-2,2′-dicarboxylic acid.[18]

The master recipe was adapted, and the reaction was performed on 1 kg scale once more. The block diagram of the alkylation is shown in Scheme 4.

The second campaign was successfully performed. Using lithium hydroxide in the hydrolysis step resulted in the desired product of a perfect quality. The saponification was completed within 5 h and afforded TDGA without salt inclusion in 96% yield.

Conclusions

In this report, the scale-up and optimisation of the synthesis of 3,4,5-tri-dodecyloxybenzoic acid has been scrutinised. The results obtained from the optimisation study, reaction calorimetry, saponification, and work-up formed a firm basis for the master recipe. The 1 kg scale synthesis of TDGA has been performed successfully (96% yield, 99% purity). The newly developed process meets all the constraints of nowadays; it is selective, highly productive, cheap, safe, and environmentally acceptable. The salt production has been reduced to a minimum.

The selected approach for process development and scale-up demonstrates some important steps, such as:

1. Definition of the important constraints for the TDGA synthesis.

2. Identification and range definition of critical process parameters.

3. Establishment of the heat and mass transfer limitations on lab-scale.

4. Verification and fine-tuning on 1 kg scale.

The insights and knowledge acquired will be used to expand the current scale-up methodology to industrial scale.

Experimental Section

All reagents and solvents were used without further purification. The water content in the solvent MIBK (4-methyl-2-pentanone, Aldrich) was analysed by a Karl Fisher titration and was within specification. All proton NMR spectra were recorded on a Varian 300 or 400 MHz spectrometer with TMS as internal standard. Mass spectra were measured on a Perseptive Voyager DE-PRO Maldi-TOF. Reaction calorimetry was performed with a Mettler-Toledo RC1*e* Reaction Calorimeter equipped with a 2 dm^3 SV01 glass reactor equipped with a pitch blade impeller. Schlummberg volumetric gas meter was used for the carbon dioxide measurements. Large-scale reaction was carried out in a 10 dm^3 fully automated (semi)batch-wise operated reactor.[7] This Belatec reactor is able to perform under a variety of conditions: a temperature range from −50 to 200 °C, solvent distillation, different agitator types, a pressure range from 0.03 to 1.1 bar. The reactor is controlled by a PLC, a special computer, which monitors physical data (batch history) and secures optimal process and safety conditions.

Representative Procedure for Methyl 3,4,5-tri-dodecyloxy-benzoate (2) for Optimisation Studies. Methyl gallate (**1**) (Fluka, 2.95 g, 16 mmol), K_2CO_3 (13.27 g, 96 mmol), tetrabutylammonium bromide (TBAB, Fluka, 0.26 g, 0.8 mmol), MIBK (40 mL) and 1-bromododecane (Acros, 12.37 g, 50 mmol), were added to a 100 mL three-necked flask. Subsequently, the reaction mixture was heated to reflux and stirred for 2 h. The conversion of the reaction was monitored by TLC (eluent hexane:ethyl acetate, 24:1) and ^{1}H NMR. Upon completion the brown mixture was cooled below 100 °C, and water (40 mL) was added. The aqueous layer was separated, and the organic layer was washed with water (40 mL), diluted HCl solution (40 mL 1.0 M), and water (40 mL) again. Solvent evaporation resulted in a yellow oil (11.7 g), which crystallises at approximately T = 40 °C into a light brown solid (**2**). Purification by column chromatography (flash SiO_2; eluent hexane:EtOAc (96:4)) yielded a white powder (10.2 g): mp 43.2−43.8 °C. ^{1}H NMR (acetone-d_6, 300 MHz): δ = 7.27 (s, 2H, *ortho*-H), 4.11−3.98 (m, 6H, OCH_2), 3.85 (s, 3H, OCH_3), 1.90−1.70 (m, 6H, $OCH_2\underline{CH_2}$), 1.55−1.20 (m, 54H, $(CH_2)_8$), 0.86 (t, 9H, CH_3). Anal. Calcd for $C_{44}H_{80}O_5$ (MW 689.12): C 76.69, H 11.70. Found: C 77.3, H 11.8.

Purification of Methyl 3,4,5-tri-dodecyloxy-benzoate (2). Crude yellow **2** (27.4 g) was heated above its melting point and poured gently into 1 L methanol (tech) under stirring. The initial yellow clusters were dispersed, and a white precipitate was formed within an hour. Filtration yielded 97% pure (based on NMR analysis) material, yield: 25.1 g = 91%.

General Procedure to Synthesise 3,4,5-Tri-dodecyloxy-benzoic acid (3). Crude yellow **2** (11.7 g) was dissolved in ethanol (96%, 40 mL) at 45 °C. Sodium hydroxide pellets (Merck, 0.77 g, 19.2 mmol) were added, and the mixture was heated to reflux. After two h of reflux, the reaction mixture was cooled and acidified with 12 M HCl solution

(18) Methyl gallate contains about 1% 4, 4′,5, 5′,6, 6′-hexakis(hydroxy)-biphenyl-2, 2′-dicarboxylic acid.

(1.7 mL, 20.4 mmol). An off-white, lumpy product precipitated from the solution at $T = 45$ °C. The precipitate was filtered and washed twice with water (40 mL) to obtain **3** (9.82 g). Crude compound **3** was taken up in CH_2Cl_2, and the insoluble inorganic salts were removed by filtration. Evaporation of the filtrate yielded the pure white solid **3** (9.5 g, 88% yield based on **1**): mp 57.5−58 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.31$ (s, 2H, *ortho*-H), 4.02 (m, 6H, OCH_2), 1.80 (m, 6H, $OCH_2\underline{CH_2}$), 1.50−1.20 (m, 54H, $(CH_2)_8$), 0.88 (t, 9H, CH_3). Anal. Calcd. for $C_{43}H_{78}O_5$ (MW 675.09): C 76.50, H 11.65. Found: C 76.51, H 11.67. Mass calcd 674.56. Found 675.59 (M + H), 697.57 (M + Na).

Master Recipe to Synthesise 3,4,5-Tri-dodecyloxybenzoic Acid (3). Methyl gallate (**1**) (Fluka, 368.3 g, 2.0 mol), ground K_2CO_3 (1660 g, 12.0 mol), tetrabutylammonium bromide (TBAB, Fluka, 32.0 g, 0.10 mol), MIBK (5.0 L), and 1-bromododecane (Acros, 1560 g, 6.26 mol) were introduced in a 10 dm^3 automated reactor. Subsequently, the reaction mixture was heated (in 20 min) to reflux and stirred (300 rpm) for 2 h. The conversion of the reaction was monitored by ^{1}H NMR. Upon completion the brown mixture was cooled to 90 °C, and water (3 L) was added. The aqueous layer was separated, and the organic layer was washed with water (3 L), with diluted HCl solution (1.5 L 1.0 M), and twice with water (2 × 1 L) again. Solvent evaporation of the organic layer resulted in a yellow−brown oil (**2**). This was kept in the reactor overnight at 45 °C under stirring (150 rpm). The oil (**2**) was dissolved in ethanol (96%, 4.8 L) and saponified with lithium hydroxide (Merck, 97.0 g, 2.3 mol) within 5 h under reflux conditions. The conversion of the reaction was monitored by ^{1}H NMR. Upon completion, the reaction mixture was cooled to 60 °C and acidified by dosing a solution of HCl (260 mL 37% HCl (Merck) diluted in 250 mL 96% ethanol) in 15 min. An off-white, lumpy product precipitated from the solution at $T = 45$ °C. The slurry was filtered and washed three times with 92% ethanol to remove residual salts. White TDGA (**3**) was obtained after drying overnight in 96% yield (1300 g) and 99% purity: mp 57.5−58 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.31$ (s, 2H, *ortho*-H), 4.02 (m, 6H, OCH_2), 1.80 (m, 6H, $OCH_2\underline{CH_2}$), 1.50−1.20 (m, 54H, $(CH_2)_8$), 0.88 (t, 9H, CH_3). Anal. Calcd for $C_{43}H_{78}O_5$ (MW 675.10): C 76.50, H 11.65. Found: C 76.47, H 11.46. Mass calcd. 674.56. Found 675.59 (M + H), 697.57 (M + Na).

Acknowledgment

This research is supported by Professor E. W. Meijer (Laboratory of Macromolecular and Organic Chemistry, TUE, Netherlands) and DSM Fine Chemicals, Netherlands. The authors gratefully acknowledge R. Hoekstra of DSM for performing the RC1 measurements and J. P. A. Custers, M. Fransen, and B. Smeets for their support in the synthesis of **2**. H. C. C. K. van Bakel of DSM Fine Chemicals is acknowledged for his assistance with the statistics. J. G. M. Moerel, H. G. Fiedler, P. H. van Eeten, and A. J. Bombeeck are acknowledged for all of their efforts and support in constructing the 10 dm^3 Belatec reactor.

Received for review June 13, 2000.

OP000066E