A Homocoupling Approach to the Key Dione of CyMe4-BTPhen – Vital Ligands for Nuclear Clean-Up by the SANEX Process

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Abstract:
CyMe4-BTPhen and CyMe4-BTBP are the principal ligand systems used in Europe for the separation of actinides from lanthanides as a part of the SANEX process for nuclear recycling and reprocessing. We present a new approach to the synthesis of the CyMe4-fragment beginning from readily available hydroxypivalic acid. It features a cobalt-catalysed homocoupling of a neopentyl bromide to provide the key bis-ester precursor, thereby avoiding the requirement for technically challenging low temperature LDA-mediated aldol chemistries.

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A Homocoupling Approach to the Key Dione of CyMe₄-BTPhen – Vital Ligands for Nuclear Clean-Up by the SANEX Process

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Abstract CyMe₄-BTPhen and CyMe₄-BTB are the principal ligand systems used in Europe for the separation of actinides from lanthanides as a part of the SANEX process for nuclear recycling and reprocessing. We present a new approach to the synthesis of the CyMe₄-fragment beginning from readily available hydroxypivalic acid. It features a cobalt-catalysed homocoupling of a neopentyl bromide to provide the key bis-ester precursor, thereby avoiding the requirement for technically challenging low temperature LDA-mediated aldol chemistries.

Key words: Homocoupling; Catalysis; Nuclear clean-up; Elemental separations; SANEX process; Accident Tolerant Fuel

Within the nuclear industry, the containment, separation, recycling, and long-term storage of radiotoxic waste is of huge importance.¹ The PUREX process separates plutonium and uranium for reuse as fuel but the remaining actinides are highly radiotoxic and long lasting (1,000s years).¹² These actinides can be transmuted by neutron fission into short-lived or stable elements thereby dramatically reducing their required storage time, however, the lanthanides must first be removed due to their high neutron capture cross-sections which interfere with the neutron fission process. This lanthanide-actinide separation is difficult due to their similar size, charge, and chemical properties³–⁸ but the University of Reading⁹,¹² has demonstrated that CyMe₄-BTPhen (1), CyMe₄-BTB and their derivatives¹¹,¹² can be used to achieve this elemental separation through a process known as SANEX.¹³–¹⁵

Whilst many modifications have been made to the ‘northern’ bipyridyl sector,¹⁶–¹⁸ alterations to the ‘southern’ triazine portion are synthetically more difficult – requiring the synthesis and subsequent condensation of the corresponding hydrazoneamide 2 and CyMe₄-dione (3). The unusual gem-dimethyl groups are required for the protection of the pseudo-benzylic position from hydrolytic degradation caused by the preponderance of hydroxy radicals in the nuclear environment.¹⁹ α-Diketones are a difficult functional group to synthesize but in our hands the acyloin cyclisation and bromine-induced oxidation (Scheme 1, bottom steps ii and iii) have proven reliable.⁹ We have previously synthesized bis-ester 4a by alkylation of ethyl iso-butyrate with bis-toyslate 5 (Scheme 1, bottom). Although yields of up to 69% are achievable, the reaction requires substantial quantities of pyrophoric n-BuLi, reaction temperatures of -20 °C and a final

Scheme 1  Retrosynthetic analysis of CyMe₄-BTPhen (1) and current route to CyMe₄-dione (3).⁹
technically challenging vacuum distillation step. With our laboratory’s continued need for larger quantities of dione 3, we desired a more scalable synthetic strategy for the synthesis of bis-ester 4a.

In devising a new approach to the CyMe₃-dione 3 we noted the symmetric nature of bis-ester 4 (Scheme 2). We believed that a metal-catalysed homocoupling reaction of 6 would provide access to this problematic compound and bromoester 6 has previously been synthesized from inexpensive hydroxy pivalic acid (7).²⁰,²¹

The bromination of hydroxy pivalic acid (Scheme 3) was very effective despite its neopentyl nature, providing bromo acid 8 in 87\%. An S₈₄ pathway is unlikely due to the unfavoured requirement of a primary cation, whilst an S₈₂ mechanism is also unlikely due to the aqueous solvent and the neopentyl system.²² We assume the effectiveness of this reaction is due to neighbouring group participation of the gem-dimethyl substituents.²³ Similar β-lactone intermediates have been isolated before, and when treated with HBr, produce the corresponding alkyl bromo acids.²⁶ The geometry of this strained intermediate 9 allows the bromide in the substitution reaction to approach more easily. The second step, a Fischer esterification, provided the ethyl ester 6a in 83\% yield and the methyl analogue 6b in 87\%.

However, when we switched to the required neopentyl system 4b (Scheme 5) our modified Ni catalyst provided no product at ambient temperature, 80 °C nor with added n-Bu₃N•H•.²⁴ We observed full consumption of the starting material but no product and suspect hydrodehalogenation followed by evaporative loss of methyl pivalate during isolation. Fortunately, the Co/Mn method allowed bis-esters 4a and 4b to be isolated in 68\% and 66\% respectively on a multi-gram scale (Scheme 5). This was achieved by ensuring the Mn was activated by sonication and TFA before use. The final two steps of acyloin cyclisation using sodium metal and oxidation progressed smoothly provided multi-gram quantities of diketone 3 – the key intermediate for the synthesis of CyMe₃-BTPhen (1).⁹

In conclusion, we have devised a new metal-catalysed homocoupling route to the important bis-ester building block (4) towards the CyMe₃-dione 3. The starting material, hydroxy pivalic acid (7) is readily available and the 3-step route is eminently scalable, technically robust (developed mainly by an undergraduate) and the raw materials are roughly half the cost of the former route (see SI). This procedure removes the need for pyrophoric reagents or cryogenic conditions on scale. More importantly, from our laboratory’s viewpoint, the challenging vacuum distillation is no longer required. This novel homocoupling of a neopentyl bromide offers a fresh approach for the synthesis of cyclic α-diketones, which could be further developed using suitable sp³–sp³ Negishi cross-couplings.³⁰ An additional advance is the use of TPTZ as an effective and cheaper alternative to terpyridine for the Ni-based homocoupling system.

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We would like to acknowledge the continued support and mentorship of Professor Laurence M. Harwood. The ATLANTIC consortium (www.atlanticconsortium.org) is thanked for the excellent discussion between disparate experts in the nuclear field.

Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

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Supplementary Information

A Homocoupling Approach to the Key Dione of CyMe₄-BTPhen – Vital Ligands for Nuclear Clean-Up by the SANEX Process

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Experimental

$^1$H-NMR spectra were recorded on Bruker DPX-400 (400 MHz) or Bruker Nanobay (400 MHz) spectrometers using tetramethylsilane (SiMe$_4$, $\delta_H = 0.00$ ppm) or DCCl$_3$ (HCCl$_3$, $\delta_H = 7.26$ ppm) as internal reference. $^{13}$C-NMR spectra were recorded on Bruker DPX-400 (101 MHz) or Bruker Nanobay (101 MHz) spectrometers using the central resonance of CDCl$_3$ (CDCl$_3$, $\delta_C = 77.16$ ppm) as the internal reference. Assignments were made using a range of NMR experiments (DEPT135, COSY, HMQC and HMBC). All chemical shifts are quoted in parts per million (ppm) down field from tetramethylsilane, measured from the centre of the signal except in the case of multiplets of more than one proton, which are quoted as a range. Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin.), multiplet (m), (ap.) apparent, (br) broad and combinations thereof.

Infrared spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer as a thin film. Letters in parentheses refer to relative absorbency of the main peak: w, weak, < 40%, m, medium, 41-74% of the main peak, s, strong >75%; and br, broad.

Accurate mass data was recorded on a V.G. Micromass 70-70F machine under chemical ionisation (CI) or under electrospray conditions on a Thermo Scientific LTQ Orbitrap XL instrument.

All reagents were used as obtained from commercial sources, unless otherwise stated. MeCN and DMF were dried using an MBraun SPS 7 solvent purifier system. Analytical thin layer chromatography (TLC) was performed using pre-coated Merck aluminum-backed silica gel plates (Silicagel 60 F254). Visualization was by UV light and/or treatment with acidic potassium permanganate, ninhydrin or acidic ammonium molybdate (IV).

![Chemical Structure](image)

3-Bromo-2,2-dimethylpropionic acid

3-Hydroxy-2,2-dimethylpropionic acid (10 g, 84.7 mmol) was dissolved in HBr (48% in H$_2$O; 100 mL) and heated to reflux (~130 °C) over-night (~18 hours). Once cooled to ambient temperature the mixture was diluted with H$_2$O (100 mL), extracted with Et$_2$O (3 x 50 mL), dried (MgSO$_4$), filtered and concentrated in vacuo to give an oil that formed a glassy solid on standing (13.4 g, 74.0 mmol, 87%). It possesses a fruity smell.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.52 (s, 2H, CH$_2$Br), 1.36 (s, 6H, 2 x Me); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 181.5 (CO), 44.2 (C), 40.8 (CH$_2$), 24.3 (CH$_3$); IR (thin film) $\nu_{\text{max}} / \text{cm}^{-1} = 2972\text{m}$(OH), 2589w, 1688s (CO), 1462m, 1388m, 1204s. HRMS submitted but no ion seen – suspected decarboxylation and subsequent elimination to isobutene.
Supplementary Information

Methyl 3-bromo-2,2-dimethylpropanoate

3-Bromo-2,2-dimethylpropanoic acid (6.0 g, 33.1 mmol) was dissolved in MeOH (100 mL) and conc. H₂SO₄ (6 mL) was added cautiously before heating under reflux for overnight (18 hours). The mixture was allowed to cool to ambient temperature and neutralised with 2 M NaOH. Most of the MeOH was removed in vacuo, the mixture was diluted with H₂O (30 mL), extracted with Et₂O (3 x 30 mL), the combined organic phases were washed with brine (50 mL), dried (MgSO₄), filtered and concentrated in vacuo to give a clear oil with a fruity smell (5.6 g, 28.8 mmol, 87%).

1H NMR (400 MHz, CDCl₃) δ 3.72 (s, 3H, OMe), 3.51 (s, 2H, CH₂Br), 1.33 (s, 6H, 2 x Me); 13C NMR (101 MHz, CDCl₃) δ 175.3 (CO), 52.3 (CH₃O), 44.1 (CH₂Br), 41.3 (CO), 24.2 (2 × CH₃), 24.2 (CH₂CH₃), 14.30 (CH₃); IR (thin film) νmax / cm⁻¹ = 3341br, 2977w, 1711s (CO), 1660w, 1477w, 1200s; HRMS submitted but no ion seen – suspected decarboxylation and subsequent elimination to isobutene.

3-Bromo-ethyl-2,2-dimethylpropanoate

3-Bromo-2,2-dimethylpropionic acid (13.4 g, 74.0 mmol) was dissolved in EtOH (130 mL) and conc. H₂SO₄ (1 mL), then heated at reflux for 18 hours. Once cooled to ambient temperature, most of the EtOH was removed in vacuo. The reaction mixture was diluted with 1:1 sat. Na₂CO₃:H₂O (100 mL), extracted with Et₂O (3 x 50 mL), dried (MgSO₄), filtered and concentrated in vacuo, to give a pale oil (12.9 g, 61.7 mmol, 83%).

1H NMR (400 MHz, CDCl₃) δ 4.17 (q, J = 7.1 Hz, 2H, OCH₂), 3.51 (s, 2H, CH₂Br), 1.31 (s, 6H, 2 x CH₃), 1.27 (t, J = 7.1 Hz, 3H, CH₃); 13C NMR (101 MHz, CDCl₃) δ 174.96 (CO), 61.17 (CH₂O), 44.10 (CH₂Br), 41.56 (C), 24.25 (CH₂CH₃), 14.30 (CH₃); IR (thin film) νmax / cm⁻¹ = 3431br, 2977w, 1711s (CO), 1660w, 1477w, 1200s; HRMS submitted but no ion seen – suspected decarboxylation and subsequent elimination to isobutene.

Diethylhexa-1,6-dioate

Cobalt Catalysis Method: CoBr₂ (0.62 g, 2.84 mmol), Mn powder (6.24 g, 114 mmol) and ethyl-3-bromopropanoate (5.14 g, 28.4 mmol) were suspended in MeCN (50 mL) under a N₂ atmosphere. CF₃CO₂H (3 drops) was then added to the stirred suspension to activate the Mn powder and after 5 min pyridine (5.7 mL, 71 mmol). The mixture was stirred until the smoke disappeared and then heated at 60...
°C for 18 h. The reaction was allowed to cool to room temperature, quenched 2 M HCl (20 mL) and stirred for 20 min. The solution was diluted with H₂O (50 mL) and extracted with Et₂O (3 x 50mL). The organic phase was washed with brine (50 mL), dried (MgSO₄), filtered and concentrated in vacuo to afford the product, a clear oil that darkened after several weeks (1.9 g, 9.44 mmol, 66%).

**Nickel Catalysis Method:** NiCl₂(H₂O)₆ (338 mg, 1.42 mmol), Zn powder (1.86 g, 28.4 mmol), ethyl-3-bromopropanoate (2.57 g, 14.2 mmol) and TPTZ (2,4,6-tris(2-pyridyl)-s-triazine) (444 mg, 1.42 mmol), were suspended in DMF (50 mL) under a N₂ atmosphere. The mixture was stirred at ambient temperature overnight. The reaction was filtered through celite, quenched 2 M HCl (20 mL) and stirred for 20 min. The solution was diluted with H₂O (50 mL) and extracted with Et₂O (3 x 50mL). The organic phase was washed with brine (50 mL), dried (MgSO₄), filtered and concentrated in vacuo to afford the product, a clear oil, that darkened after several weeks (1.17 g, 5.8 mmol, 81%).

¹H NMR (400 MHz, CDCl₃) δ 4.15 (q, 4H, J = 7.2 Hz, OCH₂), 2.34 (t, 4H, J = 6.7 Hz, CH₂), 1.68 (t, 4H, J = 6.6 Hz, CH₂), 1.26 (t, 6H, J = 6.8 Hz, CH₃); ¹³C NMR (101 MHz, CDCl₃): δC (ppm) = 173.4 (CO), 60.5 (CH₂O), 34.1 (CH₂CO), 22.4 (CH₃), 14.8 (CH₂ (γ-C to Ester)); IR (thin film) νmax/cm⁻¹ = 2980w, 1728s (CO), 1438w, 1372m, 1176s, 1028m; ESI-FTMS = Calculated C₁₀H₁₈O₄ [M+H]⁺: 225.1097; observed: 225.1094.

**Dimethyl 2,2,5,5-tetramethylhexanedioate**

CoBr₂ (225 mg, 1.1 mmol), Mn powder (2.3 g, 41 mmol) and methyl 3-bromo-2,2-dimethylpropanoate (2.0 g, 10.3 mmol) under an N₂ atmosphere were suspended in MeCN (50 mL). CF₃CO₂H (3 drops) was added with stirring to activate the Mn powder. After 5 min pyridine (2.0 mL, 25.1 mmol) was then added. The mixture was stirred until the smoke disappeared and then heated at 60 °C overnight. The reaction was allowed to cool to room temperature, quenched with 2 M HCl (20 mL) and stirred for 20 min. The solution was diluted with H₂O (50 mL) and extracted with Et₂O (3 x 50mL). The organic phase was washed with brine (50 mL), dried (MgSO₄), filtered and concentrated in vacuo to afford an off-white waxy solid (0.78 g, 3.4 mmol, 66%).

¹H NMR (400 MHz, CDCl₃) δ 3.66 (s, 6H, 2 x MeO), 1.44 (s, 4H, 2 x CH₂), 1.17 (s, 12H, 4 x CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 178.3 (CO), 51.8 (MeO), 42.2 (C), 35.8 (CH₂), 25.2 (Me); IR (thin film) νmax/cm⁻¹ = 2951w, 1729s (CO), 1624, 1474m, 1388w, 1309w, 1193s, 1136s, 1112s, 992w, 862w, 771w; ESI-FTMS = Calculated C₁₂H₂₂O₄Na [M+Na]⁺: 253.1410; observed: 253.1403.
Diethyl 2,2,5,5-tetramethylhexanedioate$^5$

Mn powder (5.0 g, 90.9 mmol) was suspended in anhydrous MeCN under a N$_2$ (g) atmosphere. CF$_3$CO$_2$H (0.2 mL) was added to activate the Mn and the vessel was sonicated for 10 mins. CoBr$_2$ (523 mg, 2.4 mmol in 10 mL MeCN) was added followed by a solution of ethyl 3-bromo-2,2-dimethylpropanoate (5.0 g, 23.9 mmol) and pyridine (5.0 mL, 60 mmol) in MeCN (15 mL). The mixture was stirred until the smoke disappeared and then heated at 60 °C overnight. The reaction was allowed to cool to room temperature, quenched 2 M HCl (100 mL) and stirred for 20 min. The solution was extracted with Et$_2$O (3 x 75 mL). The organic phase was washed with brine (100 mL), dried (MgSO$_4$), filtered and concentrated in vacuo to give a pale-yellow oil that solidified to an off-white waxy solid (2.1 g, 8.1 mmol, 68%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.12 (q, $J$ = 7.1 Hz, 4H, OCH$_2$), 1.44 (s, 4H, CH$_2$), 1.25 (t, $J$ = 7.1 Hz, 6H, CH$_2$CH$_3$), 1.15 (s, 12H, 4 x CH$_3$); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 177.9 (CO), 60.4 (CH$_2$), 42.0 (C), 35.7 (CH$_2$), 25.2 (CH$_3$), 14.4 (CH$_3$); IR (thin film) $\nu_{\text{max}}$ / cm$^{-1}$ = 3448w, 3350w, 2978m, 1288w, 1726s (CO), 1637m, 1596w, 1474w, 1387w, 1366w, 1309w, 1260w, 1189m, 1111m, 1027w; ESI-FTMS = Calculated C$_{14}$H$_{27}$O$_4$ [M+H]$^+$: 259.1904; observed: 259.1907.

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NMR Spectra

Compound 8
Compound 6a
Supplementary Information

Compound 6b
Supplementary Information

Compound 11
Compound 4b
# Cost Analysis For Synthesis of 100 g 4a

|                  | Mw  | Mol | Equiv. | Quant (g-mL) | Cost (GBP) | Cost/g | Quant (g-mL) | Cost (GBP) | Supplier   |
|------------------|-----|-----|--------|--------------|-----------|--------|--------------|-----------|------------|
| Hydroxy pivalic acid (7) | 118.1 | 1.68 | 1      | 198.0        | £35.24    | 0.178  | 1000         | £178      | Fluorochem |
| HBr (aq.)        |     |     |        | 1980.0       | £108.90   | 0.055  | 1000         | £55       | Aldrich    |
| Bromo acid (8) 82% | 181 | 1.37 |        | 248.8        |           |        |              |           |            |
| EtOH             |     |     |        | 2488.3      | £82.02    | 0.03296| 2500         | £82       | Aldrich    |
| H2SO4            |     |     |        | 9.9         | £0.04     | 0.0424 | 2500         | £106      | Aldrich    |
| Bromo ester (6a) 83% | 209 | 1.14 |        | 238.5        |           |        |              |           |            |
| CoBr2            |     | 218.7 | 0.11   | 0.1          | 25.0      | £24.46 | 0.98         | 250       | £245       | Aldrich    |
| Pyridine         | 41  | 2.85 | 2.5    | 117.0        | £13.57    | 0.116  | 1000         | £116      | Aldrich    |
| Mn               | 55  | 4.56 | 4      | 251.0        | £36.65    | 0.146  | 1000         | £146      | Aldrich    |
| MeCN anh         |     |     |        | 2384.8       | £228.94   | 0.096  | 2000         | £192      | Aldrich    |
| Dimer product (4a) 68% | 258 | 0.39 |        | 100.1        |           |        |              |           |            |

**Total Cost:** £529.82

|                  | Mw  | Mol | Equiv. | Quant (g-mL) | Cost (GBP) | Cost/g | Quant (g-mL) | Cost (GBP) | Supplier   |
|------------------|-----|-----|--------|--------------|-----------|--------|--------------|-----------|------------|
| Ethyl isobutyrate | 116 | 1.11| 1      | 129.0        | £9.03     | 0.07   | 500          | £35       | Aldrich    |
| (TsOCH2)2        | 370.4 | 0.56 | 0.5    | 206.0        | £782.63   | 3.8    | 25           | £95       | Aldrich    |
| BuLi             | 1.11 | 1    |        |              | £70.06    | 0.063  | 800          | £126      | Aldrich    |
| HN(i-Pr)2        | 101.2 | 1.22 | 1.1    | 123.8        | £4.95     | 0.04   | 1000         | £40       | Aldrich    |
| Et2O (anh)       |     |     |        | 2064.0       | £159.44   | 0.07725| 4000         | £309      | Aldrich    |
| Dimer product 70%| 258 | 0.39 |        | 100.4        |           |        |              |           |            |

**Total Cost:** £866.67