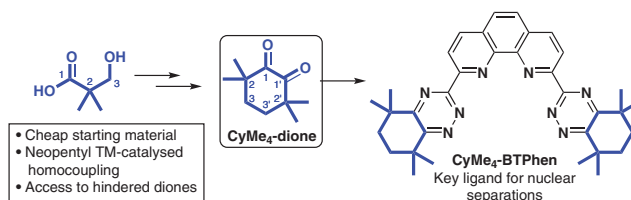


# A Homocoupling Approach to the Key Dione of CyMe<sub>4</sub>-BTPhen – Vital Ligands for Nuclear Clean-Up by the SANEX Process

Thomas M. Trunks   
 Jasraj Singh Babra   
 James Westwood  
 Christopher D. Smith\*

Department of Chemistry, University of Reading, Pepper Lane,  
 Reading, RG6 6DX, UK  
 c.d.smith@reading.ac.uk



Received: 21.12.2021

Accepted after revision: 11.01.2022

Published online: 12.01.2022

DOI: 10.1055/a-1737-8610; Art ID: so-2021-d0066-1

License terms:

© 2022. The Author(s). This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

**Abstract** CyMe<sub>4</sub>-BTPhen and CyMe<sub>4</sub>-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 CyMe<sub>4</sub> fragment beginning from readily available hydroxypivalic acid. It features a cobalt-catalysed homocoupling of a neopentyl bromide to provide the key bisester 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

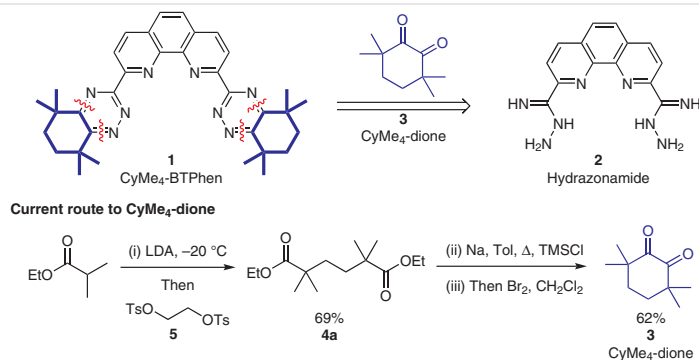
Within the nuclear industry, the containment, separation, recycling, and long-term storage of radiotoxic waste is of huge importance.<sup>1</sup> The PUREX process separates plutonium and uranium for reuse as fuel but the remaining actinides are highly radiotoxic and long lasting (thousands of years).<sup>1,2</sup> 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 interferes with the neutron fission process. This lanthanide-actinide separation is difficult due to their similar size, charge, and chemical properties<sup>3–8</sup> but the University of Reading<sup>9,10</sup> has demonstrated that CyMe<sub>4</sub>-BTPhen (**1**), CyMe<sub>4</sub>-BTBP and their derivatives<sup>11,12</sup> can be used to achieve this elemental separation through a process known as SANEX.<sup>13–15</sup>

Whilst many modifications have been made to the ‘northern’ bipyridyl sector,<sup>16–18</sup> alterations to the ‘southern’ triazine portion are synthetically more difficult – requiring the synthesis and subsequent condensation of the corresponding hydrazoneamide **2** and CyMe<sub>4</sub>-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.<sup>19</sup>  $\alpha$ -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.<sup>9</sup> We have previously synthesized bisester **4a** by alkylation of ethyl isobutyrate with bistosylate **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 technically challenging vacuum distillation step.

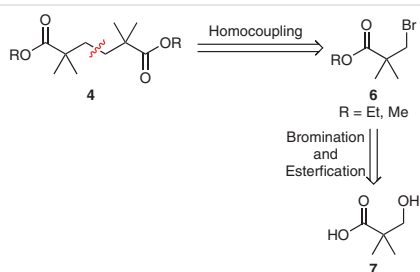
With our laboratory’s continued need for larger quantities of dione **3**, we desired a more scalable synthetic strategy for the synthesis of bisester **4a**.

In devising a new approach to the CyMe<sub>4</sub>-dione **3** we noted the symmetric nature of bisester **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**).<sup>20,21</sup>

The bromination of hydroxypivalic acid (Scheme 3) was very effective despite its neopentyl nature, providing bromo acid **8** in 87%. An S<sub>N</sub>1 pathway is unlikely due to the unfavoured requirement of a primary cation, whilst an S<sub>N</sub>2 mechanism is also unlikely due to the aqueous solvent and the neopentyl system.<sup>22</sup> We assume the effectiveness of this reaction is due to neighbouring group participation-aided formation of an intermediate  $\beta$ -lactone **9**,<sup>23,24</sup> further aided by the Thorpe–Ingold effect of the *gem*-dimethyl substitu-

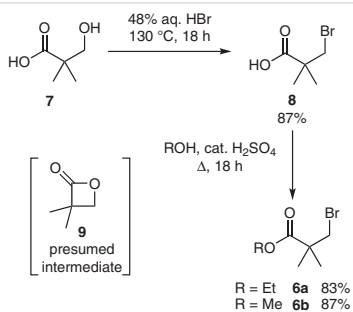


**Scheme 1** Retrosynthetic analysis of CyMe<sub>4</sub>-BTPPh (**1**) and current route to CyMe<sub>4</sub>-dione (**3**)<sup>9</sup>



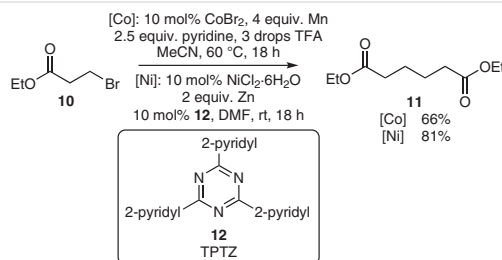
**Scheme 2** Retrosynthetic analysis of bisester **4**

ents.<sup>25</sup> Similar β-lactone intermediates have been isolated before, and when treated with HBr, produced the corresponding alkyl bromo acids.<sup>26</sup> 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%.



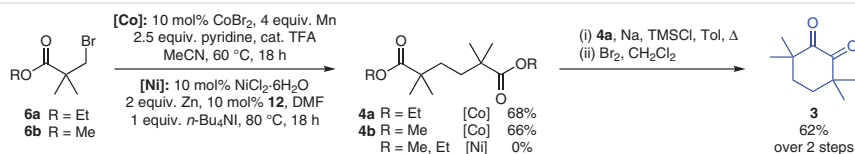
**Scheme 3** Synthetic route to the bromo ester **6**

We then looked into the sp<sup>3</sup>-sp<sup>3</sup> homocoupling step and identified cobalt<sup>27</sup> and nickel-based<sup>28</sup> catalytic systems as potential options. We used commercially available ethyl 3-bromopropanoate (**10**) as a less-hindered model system to practice our technique. The cobalt procedure<sup>27</sup> provided bisester **11** in 66% yield (Scheme 4). We made a minor modification to the Goldup/Leigh Ni system<sup>28</sup> – using TPTZ (**12**) as ligand instead of terpyridine. It is five times cheaper, presumably due to its usage as a reagent for iron analysis,<sup>29</sup> and this protocol delivered **11** in 81% yield.



**Scheme 4** Homocoupling investigations using a model system **10**

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*-Bu<sub>4</sub>N<sup>+</sup>I<sup>-</sup>.<sup>28</sup> 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 bisesters **4a** and **4b** to be isolated in 68% and 66%, respectively, on a multigram scale (Scheme 5). This was achieved by ensuring the Mn was activated by sonication and TFA before use. The



**Scheme 5** Successful Co-catalysed route to CyMe<sub>4</sub>-dione **3**

final two steps of acyloin cyclisation using sodium metal and oxidation progressed smoothly provided multigram quantities of diketone **3** – the key intermediate for the synthesis of CyMe<sub>4</sub>-BTPPhen (**1**).<sup>9</sup>

In conclusion, we have devised a new metal-catalysed homocoupling route to the important bisester building block **4** towards the CyMe<sub>4</sub>-dione **3**. The starting material, hydroxy pivalic acid (**7**) is readily available and the three-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 the Supporting Information). 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  $\alpha$ -diketones, which could be further developed using suitable sp<sup>3</sup>-sp<sup>3</sup> Negishi cross-couplings.<sup>30</sup> An additional advance is the use of TPTZ as an effective and cheaper alternative to terpyridine for the Ni-based homocoupling system.

### Conflict of Interest

The authors declare no conflict of interest.

### Funding Information

The work was supported by a grant of the Engineering and Physical Sciences Research Council (EPSRC) (EP/S011935/1, ATLANTIC: Accident ToLerANT fuels In reCycling). J.W. was supported by a grant of the Engineering and Physical Sciences Research Council (EPSRC) (EP/R014833/1, Asymmetric Catalytic Photochemistry).

### Acknowledgment

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

### Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/a-1737-8610>.

### References

- (1) *Fuel Cycle Stewardship in a Nuclear Renaissance* (October 2011), The Royal Society Science Policy Centre report 10/11, see (accessed Dec 21, 2021): [https://royalsociety.org/~media/royal\\_society\\_content/policy/projects/nuclear-non-proliferation/fuelcyclestewardshipnuclearrenaissance.pdf](https://royalsociety.org/~media/royal_society_content/policy/projects/nuclear-non-proliferation/fuelcyclestewardshipnuclearrenaissance.pdf)
- (2) Corkhill, C.; Hyatt, N. *Nuclear Waste Management*; IOP Publishing: Bristol, **2018**.
- (3) Ekberg, C.; Fermvik, A.; Retegan, T.; Skarnemark, G.; Foreman, M. R. S.; Hudson, M. J.; Englund, S.; Nilsson, M. *Radiochim. Acta* **2008**, *96*.
- (4) Dam, H. H.; Reinhoudt, D. N.; Verboom, W. *Chem. Soc. Rev.* **2007**, *36*, 367.
- (5) Kolarik, Z. *Chem. Rev.* **2008**, *108*, 4208.
- (6) Leoncini, A.; Huskens, J.; Verboom, W. *Chem. Soc. Rev.* **2017**, *46*, 7229.
- (7) Veliscek-Carolan, J. J. *Hazard. Mater.* **2016**, *318*, 266.
- (8) Bhattacharyya, A.; Mohapatra, P. K. *Radiochim. Acta* **2019**, *107*, 931.
- (9) Lewis, F. W.; Harwood, L. M.; Hudson, M. J.; Drew, M. G. B.; Desreux, J. F.; Vidick, G.; Bouslimani, N.; Modolo, G.; Wilden, A.; Sypula, M.; Vu, T.-H.; Simonin, J.-P. *J. Am. Chem. Soc.* **2011**, *133*, 13093.
- (10) Lewis, F. W.; Harwood, L. M.; Hudson, M. J.; Drew, M. G. B.; Modolo, G.; Sypula, M.; Desreux, J. F.; Bouslimani, N.; Vidick, G. *Dalt. Trans.* **2010**, *39*, 5172.
- (11) Afsar, A.; Westwood, J.; Distler, P.; Harwood, L. M.; Mohan, S.; John, J.; Davis, F. J. *Tetrahedron* **2018**, *74*, 5258.
- (12) Harwood, L. M.; Afsar, A.; Distler, P.; John, J. S.; Babra, J. Y.; Selve, Z.; Cowell, J.; Westwood, J. *Heterocycles* **2019**, *99*, 825.
- (13) Magnusson, D.; Christiansen, B.; Foreman, M. R. S.; Geist, A.; Glatz, J. P.; Malmbeck, R.; Modolo, G.; Serrano Purroy, D.; Sorel, C. *Solvent Extr. Ion Exch.* **2009**, *27*, 97.
- (14) Wilden, A.; Modolo, G.; Schreinemachers, C.; Sadowski, F.; Lange, S.; Sypula, M.; Magnusson, D.; Geist, A.; Lewis, F. W.; Harwood, L. M.; Hudson, M. J. *Solvent Extr. Ion Exch.* **2013**, *31*, 519.
- (15) Magnusson, D.; Geist, A.; Wilden, A.; Modolo, G. *Solvent Extr. Ion Exch.* **2013**, *31*, 1.
- (16) Gullede, Z. Z.; Tedder, M. L.; Lyons, K. R.; Carrick, J. D. *ACS Omega* **2019**, *4*, 18855.
- (17) Ebenezer, C.; Vijay Solomon, R. *Inorg. Chem. Front.* **2021**, *8*, 3012.
- (18) Waters, G. D.; Carrick, J. D. *RSC Adv.* **2020**, *10*, 10807.
- (19) Trumm, S.; Geist, A.; Panak, P. J.; Fanghänel, T. *Solvent Extr. Ion Exch.* **2011**, *29*, 213.
- (20) Greene, J. L.; Hagemeyer, H. J. *J. Am. Chem. Soc.* **1955**, *77*, 3016.
- (21) Ahmed, M.; Giblin, G.; Martin, P.; Myatt, J.; Norton, D.; Rivers, D. A. WO2008128951A1, **2008**.
- (22) Grunwald, E.; Winstein, S. *J. Am. Chem. Soc.* **1948**, *70*, 846.
- (23) Wiedemann, E. N.; Mandl, F. A.; Blank, I. D.; Ochsenfeld, C.; Ofial, A. R.; Sieber, S. A. *ChemPlusChem* **2015**, *80*, 1673.
- (24) Robinson, S. L.; Christenson, J. K.; Wackett, L. P. *Nat. Prod. Rep.* **2019**, *36*, 458.
- (25) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735.
- (26) Kingsbury, C. A. *J. Org. Chem.* **1968**, *33*, 3247.
- (27) Cai, Y.; Qian, X.; Gosmini, C. *Adv. Synth. Catal.* **2016**, *358*, 2427.
- (28) Goldup, S. M.; Leigh, D. A.; McBurney, R. T.; McGonigal, P. R.; Plant, A. *Chem. Sci.* **2010**, *1*, 383.
- (29) Collins, P. F.; Diehl, H.; Smith, G. F. *Anal. Chem.* **1959**, *31*, 1862.
- (30) Tungen, J. E.; Aursnes, M.; Dalli, J.; Arnardottir, H.; Serhan, C. N.; Hansen, T. V. *Chem. Eur. J.* **2014**, *20*, 14575.