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Rapid synthesis of 1,7-bis(*t*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (DO2A-*t*-Bu ester)

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Abstract

A three-step route was used to synthesize 1,7-bis(t-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (DO2A-t-Bu ester) from 1,4,7,10-tetraazacyclododecane (cyclen). The overall time of reaction was reduced from a combined ~56 h to 2.3 h with an overall yield comparable to previously reported methods.

Keywords

DO2A-*t*-Bu Ester; cyclen; transfer hydrogenation; microwave

Derivatives of 1,4,7,10-tetraazacyclododecane (cyclen), including 1,7-bis(*t*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (DO2A-*t*-Bu ester, **1**), are commonly used intermediates when synthesizing metal complexes for biomedical-related studies.[1–19] However, reported routes to synthesize and purify this intermediate require multiple days to complete.[20–22] We hypothesized that the reactions used to produce **1** could be accelerated by modification of the reaction conditions, leading to a shortened overall synthetic time while maintaining comparable yields to previously reported reactions.

The reported synthesis of DO2A-*t*-Bu ester, **1**, is carried out in three steps as depicted in Scheme 1.[20–22] First, two amines of commercially available cyclen are protected in the trans positions with a slow addition of CBZCl at 0 °C and stirring overnight.[20] Second, *t*-Bu bromoacetate is reacted with CBZ-protected cyclen, **3**, at 60 °C in the presence of diisopropylethylamine (DIEA) to produce macrocycle **4** in 20 h.[21] Finally, hydrogenation for 1 d removes the CBZ groups yielding the desired product **1**.[21]

We observed that the reaction time from **2** to **3** can be reduced with the application of heat, leading to a decrease in reaction time from 12 h to 30 min at reflux (Scheme 2).

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/. These data include detailed experimental procedures and ^{1}H- and ^{13}C-NMR spectra.

Temperatures below reflux led to either longer reaction times or lower yields. We verified that heating did not produce the undesired cis-substituted product by comparing our final product, **1**, with a reported NMR spectrum of 1,4-bis(*t*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane.[23] Based upon our observations, heating the first step at reflux leads to the exclusive formation of the trans-substituted intermediate **3**.

The reported reaction of **3** to **4** requires heating at 60 °C with 2 equiv of base for 20 h to reach completion. We predicted that the addition of excess base would allow for a shorter overall reaction time because of the similar pK_a values of DIEA and the amines on macrocycle **3** (all in the range of 9–10). Consequently, extra base should minimize protonation of the amines on **3**, allowing the desired reaction to occur. At 60 °C with a 20-fold excess of base per equivalent of **3**, this reaction took 50 min to reach completion compared to 20 h with 2 equiv of base, demonstrating that the amount of base is a key component of the reaction. To further accelerate the reaction, we heated at reflux instead of 60 °C, leading to a total reaction time of 30 min with 85% isolated yield (Scheme 2).

The final step from CBZ-protected **4** to product **1** was accelerated by transfer hydrogenation with ammonium formate and microwave irradiation. Ammonium formate is a more user-friendly reagent than H_2 gas, and similar microwave-assisted transfer hydrogenation reactions have been performed to deprotect CBZ-protected amines.[24] With the addition of ammonium formate under microwave irradiation in a sealed vessel, the reaction was complete after 10 min at 80 °C. An excess of ammonium formate was used because some sublimation was observed during the reaction, and heating above 80 °C increased the amount of sublimation that was observed. This third reaction was complete in 10 min, compared to the reported route that requires a reaction time of 1 d at room temperature with H_2 gas.

Due to the decreases in reaction times for all three steps, it is possible to synthesize DO2A-*t*-Bu ester, **1**, from commercially available cyclen in one day. We have performed the reactions leading to **1** starting from up to 5 g of cyclen with comparable yields to smaller scales, and we expect that even larger scale reactions would behave similarly.[25] Furthermore, similar yields to DO2A-*t*-Bu ester were obtained for DO2A-methyl ester and DO2A-ethyl ester. The ability to rapidly synthesize methyl, ethyl, and *t*-Bu ester variants of DO2A has the potential to greatly aid studies that use these molecules as intermediates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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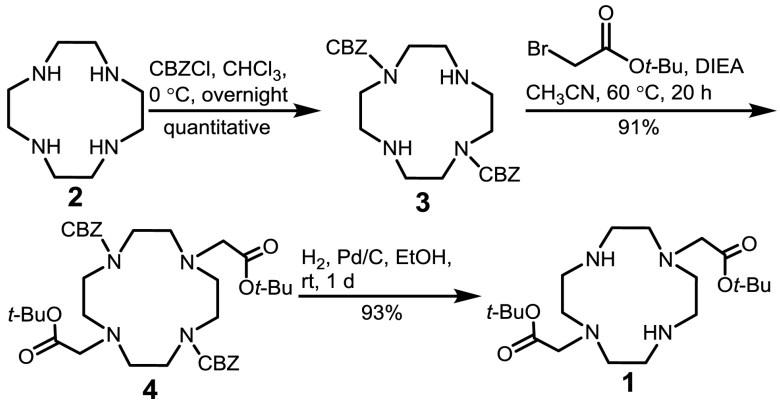
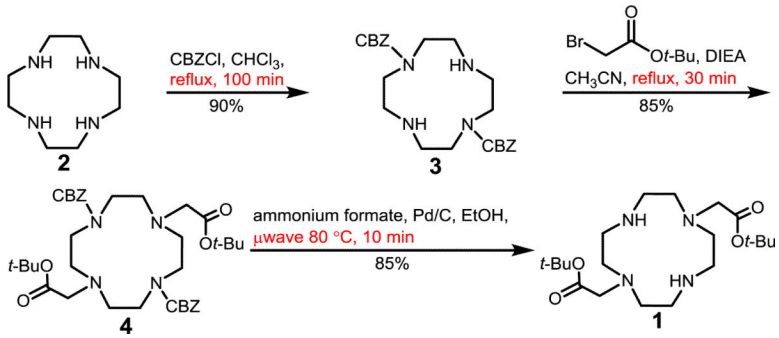
References and notes

1. Vibhute SM, Engelmann J, Verbić T, Maier ME, Logothetis NK, Angelovski G. Org. Biomol. Chem. 2013; 11:1294–1305. [PubMed: 23223612]
2. Szíjjártó C, Pershagen E, Borbas KE. Dalton Trans. 2012; 41:7660–7669. [PubMed: 22618203]
3. Polasek M, Caravan P. Inorg. Chem. 2013; 52:4084–4096. [PubMed: 23517079]
4. Que EL, New EJ, Chang CJ. Chem. Sci. 2012; 3:1829–1834. [PubMed: 25431649]
5. Shetty D, Jeong JM, Ju CH, Lee Y-S, Jeong SY, Choi JY, Yang BY, Lee DS, Chung J-K, Lee MC. Nucl. Med. Bio. 2010; 37:893–902. [PubMed: 21055619]
6. Abiraj K, Jaccard H, Kretzschmar M, Helm L, Maecke HR. Chem. Commun. 2008:3248–3250.
7. Harvey P, Chalmers KH, De Luca E, Mishra A, Parker D. Chem. Eur. J. 2012; 18:8748–8757. [PubMed: 22689478]
8. Pal R, Parker D. Org. Biomol. Chem. 2008; 6:1020–1033. [PubMed: 18327327]
9. Keizers PHJ, Saragliadis A, Hiruma Y, Overhand M, Ubbink M. J. Am. Chem. Soc. 2008; 130:14802–14812. [PubMed: 18826316]
10. Mishra A, Mishra R, Gottschalk S, Pal R, Sim N, Engelmann J, Goldberg M, Parker D. ACS Chem. Neurosci. 2014; 5:128–137. [PubMed: 24251400]
11. Peterson KL, Margherio MJ, Doan P, Wilke KT, Pierre VC. Inorg. Chem. 2013; 52:9390–9398. [PubMed: 23889495]
12. Burchardt C, Riss PJ, Zoller F, Maschauer S, Prante O, Kuwert T, Roesch F. Bioorg. Med. Chem. Lett. 2009; 19:3498–3501. [PubMed: 19477125]
13. Riss PJ, Burchardt C, Zimny MJ, Peters J, Roesch F. RSC Adv. 2012; 2:7156–7160.
14. Angelovski G, Chauvin T, Pohmann R, Logothetis NK, Tóth É . Bioorg. Med. Chem. 2011; 19:1097–1105. [PubMed: 20691598]
15. Keizers PHJ, Desreux JF, Overhand M, Ubbink MJ. Am. Chem. Soc. 2007; 129:9292–9293.
16. Law G-L, Man C, Parker D, Walton JW. Chem. Commun. 2010; 46:2391–2393.
17. Law G-L, Pal R, Palsson LO, Parker D, Wong K-L. Chem. Commun. 2009:7321–7323.
18. Parker D, Walton JW, Lamarque L, Zwier JM. Eur. J. Inorg. Chem. 2010:3961–3966.
19. Hirayama T, Taki M, Kodan A, Kato H, Yamamoto Y. Chem. Commun. 2009:3196–3198.
20. De León-Rodríguez LM, Kovacs Z, Esqueda-Oliva AC, Miranda-Olvera AD. Tetrahedron Lett. 2006; 47:6937–6940.
21. Kovacs Z, Sherry AD. J. Chem. Soc., Chem. Commun. 1995:185–186.
22. Kovacs Z, Sherry AD. Synthesis. 1997:759–763.
23. Li C, Wong W-T. J. Org. Chem. 2003; 68:2956–2959. [PubMed: 12662076]
24. Daga MC, Taddei M, Varchi G. Tetrahedron Lett. 2001; 42:5191–5194.
25. The scaled up microwave reaction was heated in an open vessel connected to a condenser located outside of the microwave cavity instead of a sealed vessel.



Scheme 1.

Reported synthesis of DO2A-*t*-Bu ester, **1**, with shortest reported times shown.[20–22]



Scheme 2.

Modified synthesis of **1** with modifications shown in red.