Research Article

Journal of Labelled Compounds and Radiopharmaceuticals

Received 22 August 2012, Revised 20 September 2012, Accepted 27 September 2012 Published online 25 October 2012 in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/jlcr.2977

Synthesis of N^1-tritylethane-1,1,2,2-d_4-1,2-diamine: a novel mono-protected C-deuterated ethylenediamine synthon

Jun Yang, Kunlun Hong, and Peter V. Bonnesen*

A convenient and high-yield synthesis for N^1-tritylethane-1,1,2,2-d_4-1,2-diamine, a novel mono-protected ethylenediamine-C-d_4, is reported. N^1-tritylethane-1,1,2,2-d_4-1,2-diamine was prepared in three steps from ethylene oxide-d_4 in a combined yield in the range 68–76%. Also reported is a synthesis of ethylenediamine-C-d_4 in two steps from 1,2-dibromoethane-d_4 in a combined yield in the range 61–65%.

Keywords: deuterated ethylenediamine; ethylenediamine-C-d_4; trityl-protected ethylenediamine-C-d_4; en-C-d_4, Mitsunobu reaction

Introduction

Ethylenediamine is a key building block in the polyamido(amine) (PAMAM) class of dendrimers.[1,2] With regard to the use of neutron scattering methods to gain more insight into the solution structure and conformations of PAMAM dendrimers, particularly of the higher (G4 and G5) generations, preparing deuterated analogs of PAMAM dendrimers is of great interest. Toward the preparation of PAMAM dendrimers in which ethylenediamine linkages are C-deuterated ($>NCD_2CD_2N<$), we were interested in methods of preparing ethylenediamine-C-d_4 by a convenient and efficient synthetic route in which one of the amine groups possessed a stable but easily cleavable protecting group.

Although ethylenediamine-C-d_4 (and derivatives such as *N*, *N*′-dibenzylethylene-C-d_4-diamine and ethylenediamine-C-d_4 dihydrochloride) and ethylenediamine-d_8 are commercially available, they are generally quite expensive, at hundreds to thousands of dollars per gram, depending on the compound. Published synthetic routes to ethylenediamine-C-d_4 (en-C-d_4) have included the synthesis of the dihydrobromide (en-C-d_4·2HBr) in excellent yields (80–90%) by direct reaction of anhydrous ammonia with 1,2-dibromoethane-d_4 in a sealed tube at 55 °C.[3] However, the reported yield on the free amine from the hydrobromide salt was low (29%). Although the Gabriel synthesis[4] was mentioned[3] as a possible route, we have not located a published procedure for en-C-d_4 using phthalimide chemistry.

Selective protection of one amine group of en-C-d_4 (such as with the *tert*-butyl carbamate or '*t*-Boc' group[5,6]) from direct reaction of the protecting reagent with en-C-d_4 using stoichiometric control invariably leads to mixtures containing unreacted diamine, mono-substituted diamine, and di-substituted diamine, and hence, yields of the desired mono-substituted product (e.g., *t*-$BocNHCD_2CD_2NH_2$) are often low (≤30%;[5,6] *t*-$BocNHCD_2CD_2NH_2$ is commercially available from for example C/D/N Isotopes Inc.). It has been reported that significantly higher yields (87%) of *t*-$BocNHCH_2CH_2NH_2$[7] can be achieved by treating ethylenediamine sequentially with one equivalent of HCl and then one equivalent of di-*tert*-butyldicarbonate, followed by neutralization. This methodology could be applied to en-C-d_4, but overall yields from a deuterated starting material such as 1,2-dibromoethane-d_4 could still be <30%.

To increase the yield of a mono-protected en-C-d_4 reagent and to conserve deuterium, we sought a means to introduce a single protecting group to one of the amine groups through an en-C-d_4 precursor molecule. We were particularly interested in the triphenylmethyl (trityl) moiety as the protecting group, as it is easily cleavable using 1N HCl, conditions that many other functionalities can tolerate. Here, we report the preparation of N^1-tritylethane-1,1,2,2-d_4-1,2-diamine in three steps from ethylene oxide-d_4, in isolated yields in the range 68–76%. We also report the two-step synthesis of en-C-d_4 from 1,2-dibromoethane-d_4 by using the Gabriel synthesis in isolated yields in the range 61–65%.

Experimental

General

All chemicals were reagent grade and used as received without further purification unless noted otherwise. The deuterated starting materials 1,2-dibromoethane-d_4 (99 atom %D) and ethylene oxide-d_4 (99.5 atom %D) were obtained from Cambridge Isotope Laboratories, Inc., Andover, MA, USA. The ethylene oxide-d_4 was received in a lecture bottle and can be used as received without further purification to make 2-(tritylamino) ethan-1,1,2,2-d_4-ol (**2**). However, because we had available in our laboratory ampoules containing ethylene oxide-d_4 that we had purified for the purpose of synthesizing deuterated poly(ethylene oxide), for convenience, we used the purified material. As a point of interest, this

Center for Nanophase Materials Sciences, Oak Ridge National Laboratory, Oak Ridge, TN 37831-6494, USA

**Correspondence to: Peter V. Bonnesen, Center for Nanophase Materials Sciences, Oak Ridge National Laboratory, Oak Ridge, TN 37831–6494, USA.*
E-mail: bonnesenpv@ornl.gov

purification involved condensing the ethylene oxide-d_4 into a round bottom flask containing calcium hydride that had been cooled to −78 °C, degassing, stirring at −10 °C for 30 min, and then distilling to a second flask containing sodium metal. After again degassing and stirring at −10 °C for 30 min, the material was distilled to a third flask containing *n*-BuLi, and the purified ethylene oxide-d_4 was finally distilled into graduated ampoules.

Proton and proton-decoupled carbon (without nuclear Overhauser effect enhancement) NMR spectra were obtained on a Varian VNMRS 500 NMR spectrometer (Palo Alto), operating at 499.72 MHz for proton. Spectra were recorded at 23 °C in either $CDCl_3$ or D_2O/TSP (TSP = sodium 3-(trimethylsilyl)propionate-2,2,3,3-d_4). Spectra recorded in $CDCl_3$ were referenced to the residual $CHCl_3$ at 7.24 ppm for proton spectra and to the center $CDCl_3$ peak at 77.23 ppm for carbon spectra; spectra recorded in D_2O/TSP were referenced to 0 ppm for TSP for both proton and carbon spectra. Elemental analysis was performed by Columbia Analytical Services, Tucson, AZ, USA.

*2-(tritylamino)ethan-1,1,2,2-d$_4$-ol (**2**)*

The following is a typical reaction. A 350-mL heavy wall glass pressure vessel was charged with trityl amine (20.0 g, 77.0 mmol), methanol (120 mL), and a stir bar. The stirred suspension was cooled to 0 °C in an ice bath. An ampoule containing ethylene oxide-d_4 (**1**, 4.5 mL, 83 mmol) also cooled to 0 °C was opened, and the contents were quickly transferred to the vessel. The vessel was sealed with a solid Teflon bushing with a Viton O-ring back seal, and the reaction mixture heated slowly to 80 °C in an oil bath (*caution*: this operation should be performed behind a shield). The mixture was stirred at this temperature for 12 h, during which time the mixture became clear and yellow. The solution was allowed to cool to room temperature, and the bushing was carefully opened behind a shield. The solution was transferred to a 500-mL round bottom flask, the solvent removed by rotary evaporation, and the crude product purified by column chromatography using a mixture of ethyl acetate and hexanes in a 1:2 volume ratio. The product was obtained as a white solid (20.88 g, 88%). M.p. 92–95 °C. ^{1}H NMR ($CDCl_3$, δ ppm): 7.55 (d, J = 7.5 Hz, 6H, $ArH^{2,6}$), 7.33 (t, J = 7.5 Hz, 6H, $ArH^{3,5}$), 7.24 (t, J = 7.5 Hz, 3H, ArH^4), 2.24 (br s, 2H, –NH and –OH). ^{13}C {^{1}H} NMR ($CDCl_3$, δ ppm): 146.0 (Ar^1), 128.7 ($Ar^{3,5}$), 128.0 ($Ar^{2,6}$), 126.5 (Ar^4), 70.7 (Ph_3C), 61.8 (p, J_{CD} = 21 Hz, $-CD_2OH$), 44.9 (p, J_{CD} = 20 Hz, $-NHCD_2-$).

*2-(2-(tritylamino)ethyl-1,1,2,2-d$_4$)isoindoline-1,3-dione (**3**)*

To a 250-mL round bottom flask were added 2-(tritylamino)ethan-1,1,2,2-d_4-ol (**2**, 5.13 g, 16.7 mmol), triphenyl phosphine (5.25 g, 20.0 mmol), phthalimide (2.95 g, 20.0 mmol), dry THF (150 mL), and a stir bar. The mixture was cooled to 0 °C with stirring, and diethyl azodicarboxylate (DEAD, 9.12 mL of a 40 wt.% solution in toluene, 20.0 mmol) was added dropwise to the mixture. At the end of the addition, the mixture was allowed to warm to ambient temperature, and stirring continued overnight. The solvent was removed by rotary evaporation, and the crude product was diluted with 150 mL $CHCl_3$ and allowed to stand at room temperature for 4 h, during which time most of the diethyl hydrazine-1,2-dicarboxylate byproduct precipitated out. The solution was filtered, and the solvent evaporated from the filtrate to leave a residue that contained both the product and triphenylphosphine oxide. Final purification was achieved by column chromatography, and the product was eluted using a mixture of ethyl acetate and hexanes in a 1:2 volume ratio. The product was obtained as white solid (6.11 g, 84%). M.p. 203–205 °C. ^{1}H NMR ($CDCl_3$, δ ppm): 7.88 (m, 2H, Phthal), 7.72 (m, 2H, Phthal), 7.41 (d, J = 7.5 Hz, 6H, $TritArH^{2,6}$), 7.19 (t, J = 7.5 Hz, 6H, $TritArH^{3,5}$), 7.13 (t, J = 7.5 Hz, 3H, $TritArH^4$), 1.82 (br s, 1H, –NH). ^{13}C {^{1}H} NMR ($CDCl_3$, δ ppm): 168.6 (C = O), 145.9 ($TritAr^1$), 134.1 ($PhthalAr^{4,5}$), 132.3 ($PhthalAr^{1,2}$), 128.5 ($TritAr^{3,5}$), 128.0 ($TritAr^{2,6}$), 126.4 ($TritAr^4$), 123.2 ($PhthalAr^{3,6}$), 70.7 (Ph_3C), 41.8 (p, J_{CD} = 20 Hz, $TritNHCD_2-$), 37.8 (p, J_{CD} = 21 Hz, $PhthalCD_2-$). Anal. Calc. for $C_{29}H_{20}D_4N_2O_4$ (%): C, 79.79; H + D, 6.46; N, 6.42; Found: C, 79.89; H + D, 6.07; N, 6.40.

*2-(2-(tritylamino)ethyl)isoindoline-1,3-dione (**3H**)*

The non-deuterated analog **3H** was prepared in an analogous manner to **3**. M.p. 201–202 °C. ^{1}H NMR ($CDCl_3$, δ ppm): 7.86 (m, 2H, Phthal), 7.71 (m, 2H, Phthal), 7.37 (d, J = 7.5 Hz, 6H, $TritArH^{2,6}$), 7.16 (t, J = 7.5 Hz, 6H, $TritArH^{3,5}$), 7.11 (t, J = 7.5 Hz, 3H, $TritArH^4$), 3.79 (t, J = 6.0 Hz, 2H, $PhthalCH_2-$), 2.45 (t, J = 6.0 Hz, 2H, $TritNHCH_2-$), 1.77 (br s, 1H, –NH). ^{13}C {^{1}H} NMR ($CDCl_3$, δ ppm): 168.7 (C = O), 145.9 ($TritAr^1$), 134.2 ($PhthalAr^{4,5}$), 132.4 ($PhthalAr^{1,2}$), 128.6 ($TritAr^{3,5}$), 128.0 ($TritAr^{2,6}$), 126.5 ($TritAr^4$), 123.4 ($PhthalAr^{3,6}$), 70.9 (Ph_3C), 42.8 ($TritNHCH_2-$), 38.7 ($PhthalCH_2-$).

*N^1-tritylethane-1,1,2,2-d$_4$-1,2-diamine (**4**)*

To a 250-mL round bottom flask were added **3** (10.0 g, pooled from several syntheses, 22.9 mmol), toluene (40 mL), absolute ethanol (80 mL), and a stir bar. The mixture was heated to reflux, and hydrazine monohydrate (6.68 mL, 138 mmol) was added into the solution using a syringe. The solution became clear, and after 30 min, a white precipitate formed. The mixture was refluxed overnight. The solution was cooled to room temperature, and the white precipitate was filtered off and washed with absolute ethanol (10 mL × 3). The solvent was removed from the combined filtrate and washings by rotary evaporation, and the product dried under vacuum. The product was obtained as white solid (6.93 g, 99%). M.p. >90 °C (decomposed). ^{1}H NMR ($CDCl_3$, δ ppm): 7.50 (d, J = 7.5 Hz, 6H, $ArH^{2,6}$), 7.27 (t, J = 7.5 Hz, 6H, $ArH^{3,5}$), 7.18 (t, J = 7.5 Hz, 3H, ArH^4) 1.58 (br s, 3H, –NH and $-NH_2$). ^{13}C {^{1}H} NMR ($CDCl_3$, δ ppm): 146.3 (Ar^1), 128.8 ($Ar^{3,5}$), 127.9 ($Ar^{2,6}$), 126.4 (Ar^4), 70.8 (Ph_3C), 45.7 (p, J_{CD} = 20 Hz, $-NHCD_2-$), 42.0 (p, J_{CD} = 20 Hz, $-CD_2NH_2$).

*2-(2-aminoethyl)isoindoline-1,3-dione hydrochloride (**5H·HCl**)*

To a 100-mL round bottom flask were added **3H** (0.60 g, 1.4 mmol), hydrochloric acid (1N, 25 mL), and a stir bar. The mixture was heated to 80 °C with stirring for 4 h, during which time triphenyl methanol precipitated out. After the mixture was cooled to room temperature, the precipitate was filtered and washed with H_2O (5 mL × 3). The water was removed from the combined filtrate and washings by rotary evaporation, leaving a white solid, which was further dried under high vacuum (0.26 g, 82%). The purity as determined by ^{1}H NMR was about 95%, with the remaining 5% consisting of a 1:1 mixture of phthalic acid and enthylenediamine dihydrochloride, produced through acid hydrolysis of the product. ^{1}H NMR (D_2O/TSP, δ ppm): 7.84 (m, 4H, Phthal), 4.02 (t, J = 5.8 Hz, $PhthalCH_2-$), 3.36 (t, J = 5.8 Hz, $-CH_2ND_3Cl$). ^{13}C {^{1}H} NMR (D_2O/TSP, δ ppm): 173.0 (C = O), 137.9 ($PhthalAr^{4,5}$), 134.0 ($PhthalAr^{1,2}$), 126.5 ($PhthalAr^{3,6}$), 41.4 ($-CH_2ND_3Cl$), 38.2 ($PhthalCH_2-$).

*2,2′-(ethane-1,1,2,2-d$_4$-1,2-diyl)diisoindoline-1,3-dione (**6**)*

To a 500-mL round bottom flask were added potassium phthalimide (53.09 g, 287 mmol), 1,2-dibromoethane-d_4 (25.0 g, 130 mmol), dimethylformamide (400 mL), and a stir bar. The mixture was stirred at 95 °C overnight. The mixture was cooled to room temperature and poured into 1-L water, precipitating a white solid. This suspension was stirred for 30 min, filtered, and the precipitate washed with water (25 mL × 3). The precipitate was dried under vacuum to afford the product as a white solid (39.15 g, 93%). M.p. 235.5–236.0 °C. ^{1}H NMR ($CDCl_3$, δ ppm): 7.80 (m, 4H, Phthal), 7.70 (m. 4H, Phthal). ^{13}C {^{1}H} NMR ($CDCl_3$, δ ppm): 168.2 (C = O), 134.0 ($PhthalAr^{4,5}$), 131.9 ($PhthalAr^{1,2}$), 123.4 ($PhthalAr^{3,6}$), 36.2 (m, J_{CD} = 22 Hz, $-CD_2\ CD_2-$).

*Ethylenediamine-C-d$_4$ (**7**)*

To a 500-mL round bottom flask were added **6** (39.15 g, 121 mmol), methanol (250 mL), and a stir bar. The mixture was stirred and heated to reflux. Hydrazine monohydrate (12.9 mL, 266 mmol) was added to the solution. The solution was refluxed overnight during which time a white precipitate formed. After the mixture was cooled to room temperature, the precipitate was filtered off and washed with methanol (10 mL × 3). The combined filtrate and washings were refluxed for 1 h over 6.5 g of CaH_2 to remove water. After filtering, the solution was fractionally distilled at atmospheric pressure, and the colorless liquid distilling at 109 °C was collected, yielding 5.57 g (91.6% w/w in methanol; 66% overall yield). ^{13}C {^{1}H} NMR ($CDCl_3$, δ ppm): 43.2 (p, J_{CD} = 20 Hz, $-CD_2CD_2-$).

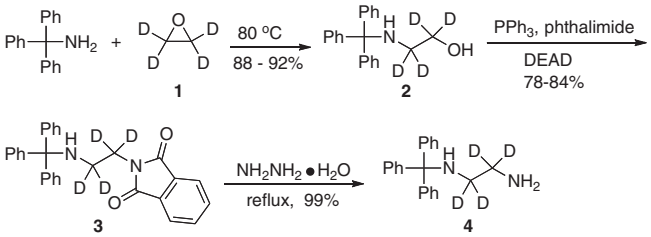
Results and discussion

Synthesis of N^1-tritylethane-1,1,2,2-d_4-1,2-diamine

The triphenylmethyl (trityl) group is a useful protecting group for primary amines[8,9] that can be easily and quantitatively removed using 1N–6N aqueous HCl and as such was suitable for our research needs. A search of the literature revealed no reports of N^1-tritylethane-1,1,2,2-d_4-1,2-diamine, but the di-deuterated analog 2-(tritylamino)ethan-*1,1*-d_2-ol has been previously reported.[10] That material was synthesized in two steps by the reaction of trityl chloride with ethyl glycine ester hydrochloride, followed by reduction of the ester carbonyl with lithium aluminum deuteride. In our case, to obtain the $-CD_2CD_2-$ linkage, we used the ring opening reaction of trityl amine with commercially available ethylene oxide-d_4 to obtain 2-(tritylamino)ethan-1,1,2,2-d_4-ol (**2**) (Scheme 1), knowing that we could convert the pendant hydroxyl functionality to an amine using Mitsunobu chemistry[11] in combination with the Gabriel reaction.[4]

For the synthesis of **2**, the reaction was performed in a sealed heavy-walled vessel capable of handling up to 80 PSI, because the reaction temperature of 80 °C needed for the nucleophilic ring opening of the epoxide[12] is well above the 9 °C boiling point of ethylene oxide-d_4. Following purification by column chromatography, **2** can be obtained as a white solid with a 92–95 °C melting point, with isolated yields typically in the 88–92% range (reported in the Experimental Section is the largest scale reaction performed, which provided **2** in 88% yield). The ^{1}H NMR of **2** showed resonances associated with the phenyl protons of the trityl group, plus a broad singlet at 2.24 ppm that represented both the –NH– and –OH resonances. The ^{13}C NMR featured the two deuterated carbons as pentets, with C-D coupling constants of 21 Hz for $-CD_2OH$ (centered at 61.8 ppm) and 20 Hz for $-NHCD_2-$ (centered at 44.9 ppm); these coupling constants are similar to those reported for other molecules containing the NCD_2CD_2N group.[13]

Alcohol **2** was converted to amine **4** in two steps using the Mitsunobu and Gabriel reactions. For the preparation of the phthalimide intermediate **3**, a 20% excess of triphenylphosphine, phthalimide, and diethyl azodicarboxylate (DEAD) were used to drive the conversion of **2** to **3**. After purification by column chromatography, product **3** is obtained as a white solid with a 203–205 °C melting point, with isolated yields typically in the 78–84% range. The ^{13}C NMR again featured the deuterated carbons as pentets with C-D coupling constants of 20 Hz for the carbon (centered at 41.8 ppm) on the side attached to the trityl group, and 21 Hz for the carbon (centered at 37.8 ppm) on the side possessing the phthalimide group. For the non-deuterated analog 2-(2-(tritylamino)ethyl)isoindoline-1,3-dione (**3H**), which to the best of our knowledge has not previously been reported in the literature, the ^{1}H NMR spectrum is very similar to that of **3**, except of course for the presence of the two triplet resonances at 3.79 and 2.45 ppm, respectively, for the PhthalCH_2- and TritNHCH_2- protons. In the ^{13}C NMR, the PhthalCH_2- and TritNHCH_2- are singlets and are shifted slightly (~1 ppm unit) downfield relative to deuterated **3** at, respectively, 38.7 and 42.8 ppm.



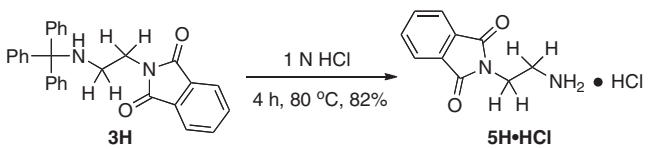
Scheme 1. Synthesis of N^1-tritylethane-1,1,2,2-d_4-1,2-diamine (**4**).

Because **3** is ethylenediamine-C-d_4 bearing dissimilar protecting groups at the two amine termini, in principle, either the phthalimide group or the trityl group can be cleaved to afford the trityl– or phthalimide– mono-protected ethylenediamine-C-d_4. Cleaving the phthalimide group by heating **3** with excess hydrazine monohydrate in a 2:1 vol/vol mixture of ethanol and toluene affords the title compound N^1-tritylethane-1,1,2,2-d_4-1,2-diamine (**4**) as a white solid in high purity at nearly quantitative yield (typically 99%). Similar to **2** and **3**, the ^{13}C NMR showed two pentet signals for the two $-CD_2-$ groups; however, for this compound, the J_{CD} was 20 Hz in both cases, with the pentets centered at 45.7 ppm (TritNHCD_2-) and 42.0 ppm ($-CD_2NH_2$). The combined yield for the three steps for preparing N^1-tritylethane-1,1,2,2-d_4-1,2-diamine from ethylene oxide-d_4 is in the 68–76% range.

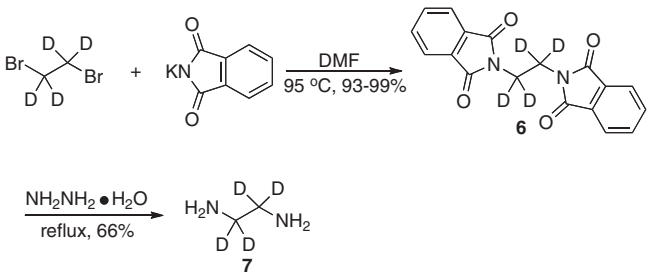
For our purposes, **4** was the desired synthon; however, if the phthalimide-protected ethylenediamine-C-d_4 is desired instead, **3** could be treated with 1N HCl to cleave the trityl group to afford 2-(2-aminoethyl-1,1,2,2-d_4)isoindoline-1,3-dione (**5**) as the stable hydrochloride **5·HCl**. To test this option, we performed the reaction on the hydrogen version **3H** (Scheme 2) by heating a solution of **3H** in 1N aqueous HCl at 80 °C for 4 h. After cooling, the solution was filtered to remove the insoluble triphenyl methanol that precipitated. Removal of the water from the aqueous filtrate afforded 2-(2-aminoethyl)isoindoline-1,3-dione hydrochloride, **5H·HCl**, at a purity of 95%, in 82% yield. Acid hydrolysis of the phthalimide group is a competing side reaction, and the remaining 5% of the product was a 1:1 mixture of phthalic acid and ethylenediamine dihydrochloride. Hence, this reaction would need to be monitored carefully to avoid excessive hydrolysis of the phthalimide group.

Synthesis of ethylenediamine-C-d_4

Although the Gabriel synthesis[4] had been mentioned[3] as a possible route to en-C-d_4, it appears that no detailed procedure for preparing en-C-d_4 using phthalimide chemistry has been reported in the literature. We did find the Gabriel synthesis to be a useful route for preparing en-C-d_4 in two steps from commercially available 1,2-dibromoethane-d_4. Reaction of 1,2-dibromoethane-d_4 with a 10% excess of potassium phthalimide in dimethylformamide at 95 °C overnight, followed by pouring the cooled solution into a large volume of water, afforded the intermediate 2,2′-(ethane-1,1,2,2-d_4-1,2-diyl)diisoindoline-1,3-dione **(6)** as a white precipitate in high (93–99%) yields (Scheme 3). The product **6** is a shelf-stable white solid with a melting point in the range 235.5–236.0 °C, which can be used to generate en-C-d_4 (**7**) as needed.



Scheme 2. Conversion of **3H** to 2-(2-aminoethyl)isoindoline-1,3-dione hydrochloride (**5H·HCl**).



Scheme 3. Synthesis of ethylenediamine-C-d_4 (**7**).

Removal of the phthalimide groups to convert **6** to **7** was performed using hydrazine monohydrate in a manner similar to that described for converting **3** to **4**, except that the stoichiometric amount (two equivalents) of hydrazine monohydrate required was used rather than an excess, and the reaction was performed in pure methanol rather than the 2:1 ethanol : toluene mixture, to facilitate the isolation of **7** via fractional distillation. Nevertheless, it is difficult to obtain **7** completely methanol-free without sacrificing yield, and typically, the ethylenediamine-C-d_4 is obtained as a ~9:1 mixture with methanol, in 66% product yield, giving a combined yield from 1,2-dibromoethane-d_4 of 61–65%. Fully deuterated ethylenediamine-d_8 can be obtained from ethylenediamine-C-d_4 following the method reported for converting ethylenediamine to ethylenediamine-N-d_4 via exchange with D_2O, followed by treatment with sodium metal at −78 °C.[14]

Summary

A procedure for preparing N^1-tritylethane-1,1,2,2-d_4-1,2-diamine, **4**, a novel mono-protected ethylenediamine-C-d_4, in three steps from ethylene oxide-d_4 in a combined yield in the range 68–76%, has been successfully developed. This compound can be a useful way for introducing the en-C-d_4 moiety, where subsequent mild deprotection conditions (e.g., 1N HCl) are needed. Also described is a synthesis of en-C-d_4 in two steps from 1,2-dibromoethane-d_4 in combined yields in the range 61–65%.

Acknowledgements

This research was conducted at the Center for Nanophase Materials Sciences, which is sponsored at the Oak Ridge National Laboratory by the Scientific User Facilities Division, Office of Basic Energy Sciences, US Department of Energy. This manuscript has been authored by UT-Battelle, LLC, under Contract No. DE-AC05-00OR22725 with the US Department of Energy. The publisher, by accepting the article for publication, acknowledges that the United States Government retains a non-exclusive, paid-up, irrevocable, world-wide license to publish or reproduce the published form of this manuscript, or allow others to do so, for United States Government purposes.

Conflict of Interest

The authors did not report any conflict of interest.

References

[1] D. A. Tomalia, H. Baker, J. Dewald, M. Hall, G. Kallos, S. Martin, J. Roeck, J. Ryder, P. Smith, *Polym. J.*, **1985**, *17*, 117–132.
[2] D. A. Tomalia, A. M. Naylor, W. A. Goddard III, *Angew. Chem. Int. Ed Engl.* **1990**, *29*, 138–175.
[3] R. W. Gaver, R. K. Murmann, *J. Inorg. Nucl. Chem.* **1964**, *26*, 881–885.
[4] S. Gabriel, *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 2224–2236.
[5] E. Fontana, A. Pignatti, *J. Labelled Compd. Radiopharm.* **2002**, *45*, 899–909.
[6] B. J. Wolfe, F. Ghomashchi, T. Kim, C. A. Abam, M. Sadilek, R. Jack, J. N. Thompson, C. R. Scott, M. H. Gelb, F. Turecek, *Bioconjugate Chem.* **2012**, *23*, 557–564.
[7] D. W. Lee, H.-J. Ha, W. K. Lee, *Synth. Commun.* **2007**, *37*, 737–742.
[8] A. N. Acharya, A. Nefzi, J. M. Ostresh, R. A. Houghten, *J. Comb. Chem.* **2001**, *3*, 189–195.
[9] K. E. Krakowiak, J. S. Bradshaw, *Synth. Commun.* **1998**, *28*, 3451–3459.
[10] J. J.-H. Wang, K. K. Chan, *J. Labelled Compd. Radiopharm.* **1996**, *38*, 105–115.
[11] O. Mitsunobu, M. Wada, T. Sano, *J. Am. Chem. Soc.* **1972**, *94*, 679–680.
[12] M. Soroka, W. Goldeman, *Arkivoc*, **2003**, 31–37.
[13] I. A. Fallis, D. M. Murphy, D. J. Wilcox, R. J. Tucker, R. D. Farley, R. Jenkins, R. R. Strevens, *J. Am. Chem. Soc.* **2004**, *126*, 15660–15661.
[14] J. H. Wotiz, P. M. Barelski, D. F. Koster, *J. Org. Chem.*, **1973**, *38*, 489–493.