A Highly Selective Mono-C-allylation of DTPA Pentaethyl Ester

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Abstract: A highly selective mono-C-allylation of pentaethyl diethylenetriaminepentaacetate was achieved with allyl bromide and potassium carbonate via a newly developed elaborate procedure based on Stevens rearrangement. It is contrastive that the conservative one-pot procedure gave a complicated mixture.

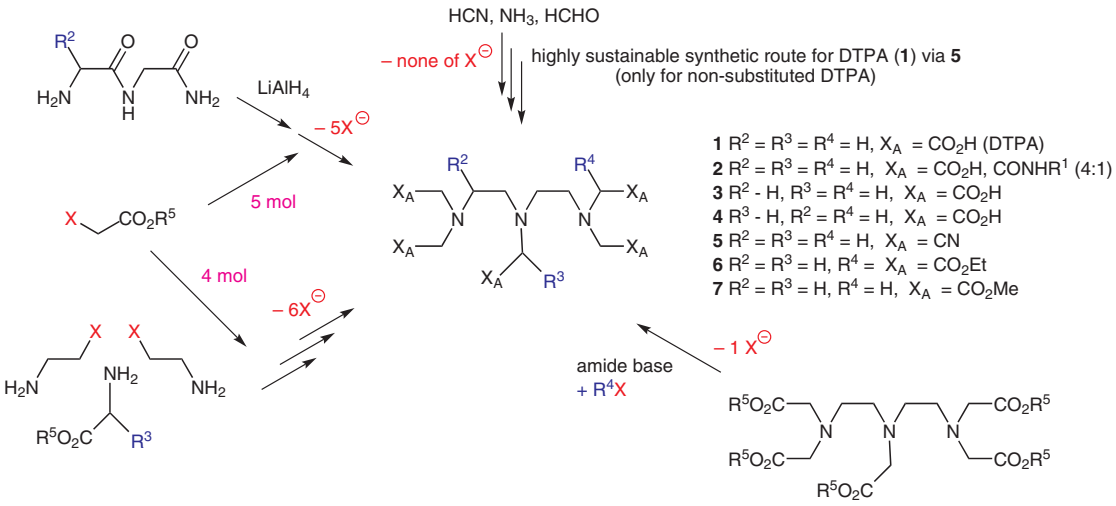
Key words: MRI, Stevens rearrangement, chelating agent, Mizoroki–Heck reaction

Diethylenetriaminepentaacetic acid (DTPA, **1**) is a well-known chelating agent of heavy-metal cations (Scheme 1).[1] To design the hybrid molecules possessing both a peculiarity of the metal cations and an orthogonal property such as a specific affinity for particular organs or cells, a number of DTPA derivatives have been synthesized.[2–5,7,8] A major molecular design is shown as **2**, which can be synthesized from commercially available DTPA dianhydride and an amine (H_2NR^1). Despite the simplicity of this synthetic strategy, it should be reconsidered; the loss of one of the five carboxylates decreases the binding ability.[3,9]

Recently, syntheses of DTPA derivatives with five free carboxylates that contain a linker-and-functionality group at a carbon of the framework, such as in **3** and **4**, have been reported via a number of C–N bond-formation reactions.[4] The loss of large amounts of halogen salts, however, makes these processes unsustainable.

In contrast, fundamental molecule **1** has been prepared in a highly sustainable industrial-scale process via addition–dehydration reactions followed by hydrolysis of pentanitrile **5**.[6] We recently developed a carbon–carbon bond-forming reaction that enables addition of a side chain directly onto the DTPA framework to afford **6**.[5] However, poor reproducibility on a large scale has remained problematic. In this process, highly moisture- or air-sensitive carbanion species must be generated with strict stoichiometric control because of the five reacting groups in the DTPA framework. Similar procedures were reported by Keana et al.[7] and Muller et al.[8] to afford **7** in only 32–36% yield. Accordingly, the efficient methods for the synthesis of DTPA-hybrid molecules have not yet been developed.

In this paper, we report a highly practical and reproducible mono-C-allylation reaction of **8**[5] using allyl bromide (**9**) in DMF in the presence of potassium carbonate (K_2CO_3) as an essential base (Scheme 2). Importantly, excessively strict control of the quantity of each reagent is not required. It is believed that this key reaction proceeds via the Stevens rearrangement,[10] N-allylation followed by C-migration.[11] However, results of our preliminary attempts, conservative procedures of Stevens rearrangement reported in a number of previous papers,[10] were described at



Scheme 1 Previous synthetic routes of DTPA derivatives for candidates of MRI agents

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first for comparison. Those conservative procedures were the same as a newly developed condition except 'one-pot' and 'stepwise'. The conservative conditions gave mixtures of mono-C-allylated products **10** and **11**, recovered **8**, and an unidentified complex mixture of byproducts **12**–**14** (likely di- and triallylated compounds) were obtained in irreproducible yields. The values of chemical yield shown in Scheme 2 are the best of all we have attempted by the conservative procedure. Although the reaction procedure was easy and simple, isolated yield of the desired one was low, and it was very unpractical to purify the desired one in pure form.

In contrast, the newly developed elaborate procedure reported herein gave **10**[12] in 63% isolated yield along with **11**[12] and **8** in 5% and 10% yields, respectively. The chemical yield and selectivity were significantly increased by inserting a 'vacuum operation' between the N-allylation[13] and C-migration steps. First, a mixture of **8** and nine equivalents of **9** was heated in DMF without base for 39 hours. The mixture was then concentrated in vacuo to exhaustively remove any excess **9**. The residue was dissolved in DMF, and K_2CO_3 was added. Heating the suspension with stirring for 70 hours afforded **10** with high selectivity.[14,15] This procedure was highly reproducible even when 50 grams of **8** were used.

It is noteworthy that the central-selectivity of our new procedure contrasts with the edge-selectivity of the carbon–carbon bond-forming reaction that afforded **6**[5] and **7**.[7,8] We propose that the central nitrogen is more nucleophilic than the two edge nitrogens because it has only one electronegative substituent (CH_2CO_2Et), while edge nitrogens have two (Figure 1). The higher nucleophilicity increases the central nitrogen's ability to form an ammonium cation.

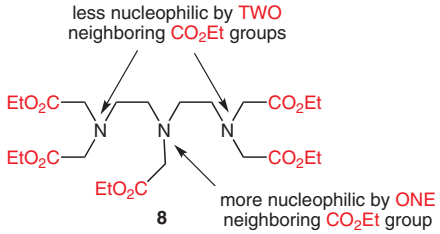
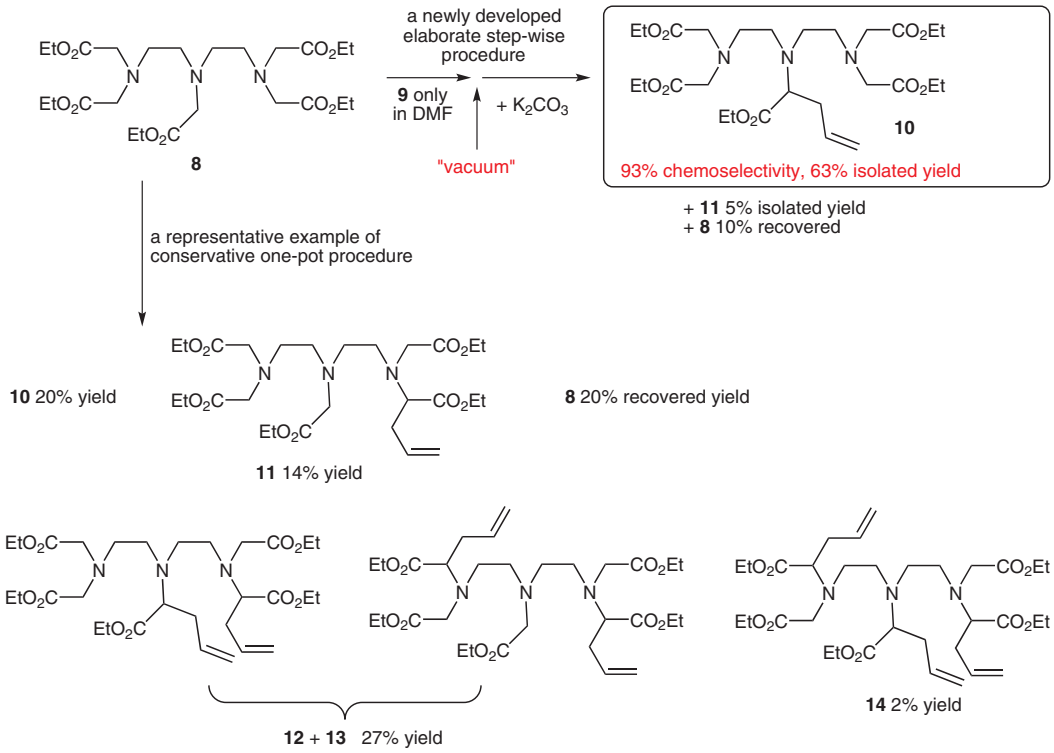


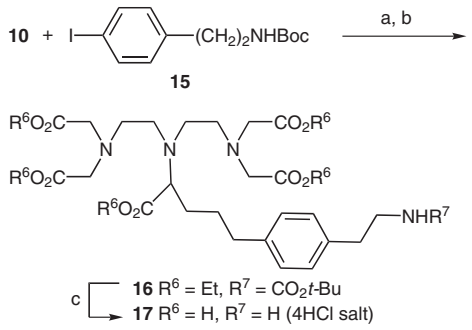
Figure 1 Considerable difference of nucleophilicity between the central nitrogen atom and the edge nitrogen atoms

Compound **10** was then further reacted to form a DTPA-hybrid molecule (Scheme 3). Via the Mizoroki–Heck reaction,[16] the allylic moiety of **10** was converted to a linker-and-functionality group using aryl iodide **15**,[17] which was hydrogenated to afford **16** in 84% overall yield. Acid hydrolysis of **16** led to formation of the hydrochloride salt of all-carboxylate-free DTPA derivative **17**[18] bearing an amino terminal group in 92% yield.

In conclusion, we have developed a highly selective mono-C-allylation reaction for functionalizing the DTPA framework via an elaborately modified Stevens rearrangement and demonstrated the synthesis of a DTPA derivative bearing a linkage and functionality at the central carbon atom. Detail exploration of the mechanism of the allylation reaction and synthesis of various key synthetic intermediates such as **17** are now in progress.



Scheme 2 A representative example of conservative one-pot procedure and a newly developed elaborate procedure of mono-C-allylation of **8**. *Reagents and conditions*: a) allyl bromide (**9**), DMF, 40 °C, 39 h; then evaporation for removal of allyl bromide; b) K_2CO_3, DMF, 70 h, 80 °C.



Scheme 3 Synthesis of a DTPA derivative bearing amino terminal group at C-branched side chain. *Reagents and conditions*: a) $Pd(OAc)_2$, P(*o*-Tol)$_3$, *i*-Pr_2NEt, MeCN–H_2O, 60 °C, 8 h, 87% yield; b) Pd/C, H_2, EtOH, r.t., 11 h, 97% yield; c) aq HCl (4.1 mol/L)–THF (4:1), reflux, 12.5 h, 92% yield. Boc = *tert*-butoxycarbonyl.

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(12) **Analytical Data for Compound 10**
Colorless oil. FT-IR (neat): 3628, 3448, 3077, 2981, 2366, 2055, 1732, 1642, 1446, 1370, 1343, 1188, 1029, 917, 856, 808, 733 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.80 (ddt, *J* = 16.8, 10.0, 6.8 Hz, 1 H, inside of terminal olefin), 5.08 (d, *J* = 16.8 Hz, 1 H, an edge of terminal olefin), 5.03 (dt, *J* = 10.0, 0.4 Hz, 1 H, an edge of terminal olefin), 4.20–4.13 (m, 10 H, 5 × OCH_2CH_3), 3.57 (s, 8 H, 4 × NCH_2CO_2Et), 3.50 (t, *J* = 7.6 Hz, 1 H, allyl-$CHCO_2Et$), 2.88–2.77 [m, 6 H, $N(CH_2CH^AN)_2$], 2.71–2.66 [m, 2 H, $N(CH_2CH^BN)_2$], 2.51 (ddd, *J* = 14.0, 7.6, 6.8 Hz, 1 H, $CH^ACH{=}CH_2$), 2.35 (ddd, *J* = 14.0, 7.6, 6.8 Hz, 1 H, $CH^BCH{=}CH_2$), 1.285 (t, *J* = 6.8 Hz, 12 H, 4 × OCH_2CH_3), 1.276 (t, *J* = 6.8 Hz, 3 H, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2 (C), 170.9 (4 × C), 134.9 (CH, olefinic), 116.5 (CH_2, olefinic), 63.6 (CH, allyl-$CHCO_2Et$), 60.2 (4 × CH_2, OCH_2CH_3), 60.0 (CH_2, OCH_2CH_3), 55.1 (4 × CH_2, NCH_2CO_2Et), 53.3 [2 × CH_2, $N(CH_2CH_2N)_2$], 50.2 [2 × CH_2, $N(CH_2CH_2N)_2$], 34.3 (CH_2, $CH_2CH{=}CH_2$), 14.3 (CH_3, OCH_2CH_3), 14.1 (4 × CH_3, OCH_2CH_3). ESI-HRMS: *m/z* $[M + H]^+$ calcd for $C_{27}H_{48}O_{10}N_3$: 574.3340; found: 574.3331.
Analytical Data for Compound 11
Colorless oil. FT-IR (neat): 3626, 3542, 3453, 3077, 2981, 2938, 2907, 2873, 2386, 2350, 2057, 1883, 1731, 1643, 1465, 1446, 1371, 1344, 1189, 1029, 919, 861, 807, 725, 574 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.83 (ddt, *J* = 16.8, 10.0, 6.8 Hz, 1 H, inside of terminal olefin), 5.08 (d, *J* = 16.8 Hz, 1 H, an edge of terminal olefin), 5.03 (d, *J* = 10.0 Hz, 1 H, an edge of terminal olefin), 4.19–4.12 (m, 10 H, 5 × OCH_2CH_3), 3.60–3.45 (m, 9 H, 4 × NCH_2CO_2Et and allyl-$CHCO_2Et$), 2.90–2.77 [m, 8 H, $N(CH_2CH_2N)_2$], 2.49 (ddd, *J* = 10.0, 6.8, 6.8 Hz, 1 H, $CH^ACH{=}CH_2$), 2.40 (ddd, *J* = 10.0, 6.8, 6.8 Hz, 1 H, $CH^BCH{=}CH_2$), 1.29–1.26 (m, 15 H, 5 × OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3 (C), 171.7 (C), 171.4 (C), 171.1 (2 × C), 134.5 (CH, olefinic), 116.9 (CH_2, olefinic), 64.3 (CH, allyl-$CHCO_2Et$), 60.43 (2 × CH_2, CH_2, OCH_2CH_3), 60.40 (CH_2, OCH_2CH_3), 60.3 (CH_2, OCH_2CH_3), 60.2 (CH_2, OCH_2CH_3), 55.3 (2 × CH_2, NCH_2CO_2Et), 55.1 (CH_2, NCH_2CO_2Et), 53.2 (CH_2, NCH_2CO_2Et), 52.8 (CH_2, NCH_2CH_2N), 52.7 (CH_2, NCH_2CH_2N), 52.3 (CH_2, NCH_2CH_2N), 50.7 (CH_2, NCH_2CH_2N), 34.9 (CH_2, $CH_2CH{=}CH_2$), 14.5 (CH_3, OCH_2CH_3), 14.34 (CH_3, OCH_2CH_3), 14.31 (2 × CH_3, OCH_2CH_3), 14.28 (CH_3, OCH_2CH_3). ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $C_{27}H_{47}O_{10}N_3Na$: 596.3159; found: 596.3152.

(13) During the reaction of **8** (retention time t_R = 0.91 min) and **9** in DMF without K_2CO_3, a newly generated peak (t_R = 1.24 min) was observed by UPLC® [BEH C_{18} 1.7 μm column (2.1 mm id. × 50 mm length), linear gradient of MeCN (0.1% TFA) in H_2O (0.1% TFA), 40–50% over 5 min, detected by UV at 220 nm]. The new peak was disappeared after the addition of K_2CO_3, and **10** (t_R = 1.65 min) was produced. Accordingly, the new peak may indicate the generation of N-allylated ammonium intermediate (s). Unfortunately,

purification of the intermediate (s) was unsuccessful because of the instability. HPLC separation afforded a mixture of unidentified polar materials along with unreasonably small amounts of **8**.

(14) **Details of Initial Conditions until Optimization**
Under the same conditions except for the amount of **9**, **10** was obtained in 23% with 3.0 equiv, 36% with 5.0 equiv, 55% with 7.0 equiv, 63% with 9.0 equiv, 62% with 10.0 equiv, 63% with 11.0 equiv, and 61% yield with 12.0 equiv. Thus, the use of 9 equiv of **9** was adequate. When the reaction period of the first process (N-allylation) was shorter than 39 h, not only was the recovery yield of **8** pointlessly increased, but the formation of unignorable amount of isomers **11**, di- and tri-allylated compounds was also observed. At this moment, we considered that N-allylation is reversible and the mono-(central-N)-allylated cation to afford **10** is thermodynamically most stable of all the other N-allylated ammonium cations. The final process (C-migration) was terminated when the peak corresponding to the N-allylated cations by UPLC® was disappeared. The reaction at higher temperature than 80 °C gave a larger amount of unidentified polar materials. At lower temperature than 80 °C, much longer reaction period was required to consume the N-allylated intermediates.

(15) When we attempted the same reaction with crotyl bromide, a mixture of inseparable complicated compounds was obtained probably because of the presence of various isomers. Accordingly, the selectivity (α- or γ-selectivity of C–N bond formation for the first step and [2,3]- or [1,2]-sigmatropy for the second step) could not be discussed.

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(18) **Analytical Data for Compound 16**
Colorless oil. FT-IR (neat): 3627, 3396, 2980, 2367, 2054, 1733, 1699, 1508, 1164, 868, 810, 775 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.10 (s, 4 H, arom.), 4.62–4.52 (m, 1 H, N*H*Boc), 4.18–4.11 (m, 10 H, 5 × O$CH_2$$CH_3$), 3.54 (s, 8 H, 4 × N$CH_2$$CO_2$Et), 3.39–3.33 (m, 3 H, N$CH$$CO_2$Et and CH_2NHBoc), 2.86–2.56 [m, 12 H, N($CH_2$$CH_2$N)$_2$ and $CH_2$$C_6H_4$$CH_2$], 1.80–1.56 (m, 4 H, NCH$CH_2$$CH_2$), 1.44 [s, 9 H, C($CH_3$)$_3$], 1.258 (t, *J* = 7.2 Hz, 12 H, 4 × O$CH_2$$CH_3$), 1.250 (t, *J* = 7.2 Hz, 3 H, O$CH_2$$CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9 (C, O*C*=O), 170.8 (4 × C, O*C*=O), 155.5 (C, N*C*=O), 139.9 (C, arom.), 136.0 (C, arom.), 128.4 (2 × CH, arom.), 128.2 (2 × CH, arom.), 78.6 (C, O*C*Me$_3$), 63.4 (CH, N*C*HCO_2Et), 60.0 (4 × CH_2, O$CH_2$$CH_3$), 59.7 ($CH_2$, O$CH_2$$CH_3$), 54.9 (4 × CH_2, N$CH_2$$CO_2$Et), 53.4 [2 × CH_2, N($CH_2$$CH_2$N)$_2$], 50.0 [2 × CH_2, N($CH_2$$CH_2$N)$_2$], 41.5 ($CH_2$, CH_2NHBoc), 35.5 (CH_2, one of $CH_2$$CH_2$$CH_2$$C_6H_4$$CH_2$), 34.9 ($CH_2$, one of $CH_2$$CH_2$$CH_2$$C_6H_4$$CH_2$), 29.3 ($CH_2$, one of $CH_2$$CH_2$$CH_2$$C_6H_4$$CH_2$), 28.1 (3 × CH_3C(CH_3)$_3$], 27.9 (CH_2, one of $CH_2$$CH_2$$CH_2$$C_6H_4$$CH_2$), 14.1 ($CH_3$, O$CH_2$$CH_3$), 13.9 (4 × CH_3, O$CH_2$$CH_3$). ESI-HRMS: *m/z* [M + H]$^+$ calcd for $C_{40}H_{67}N_4O_{12}$: 795.4755; found: 795.4746.

Analytical Data for Compound 17
Hygroscopic colorless solid. FT-IR (KBr): 3420, 2955, 2361, 1734, 1647, 1636, 1507, 1457, 1418, 1214, 1057, 954, 899, 814, 667 cm^{-1}. ^1H NMR (400 MHz, D_2O, $TMSCH_2CH_2CO_2Na$ as an internal standard): δ = 7.28 (d, *J* = 7.2 Hz, 2 H, arom.), 7.26 (d, *J* = 7.2 Hz, 2 H, arom.), 3.96 (s, 8 H, 4 × N$^+$C$H_2$$CO_2$D), 3.56–3.53 (m, 1 H, N$^+$C*H*$CO_2$D), 3.43 [t, *J* = 6.8 Hz, 4 H, N$^+$(CH_2CH_2N$^+$)$_2$], 3.26 (t, *J* = 6.8 Hz, 2 H, CH_2N$^+$D$_3$], 3.19–3.09 [m, 4 H, N$^+$($CH_2$$CH_2N^+$)$_2$], 2.97 (t, *J* = 6.8 Hz, 2 H, C_6H_4C$H_2$$CH_2N^+D_3$), 2.67 (t, *J* = 6.8 Hz, 2 H, $CH_2$$CH_2CH_2$$C_6H_4$), 1.87–1.78 (m, 1 H, C*H*^{A}$CH_2$$CH_2$$C_6H_4$), 1.76–1.69 (m, 2 H, CH_2C$H_2$$CH_2$$C_6H_4$), 1.64–1.58 (m, 1 H, C*H*^{B}$CH_2$$CH_2$$C_6H_4$). ^{13}C NMR (100 MHz, D_2O, $TMSCH_2CH_2CO_2Na$ as an internal standard): δ = 177.8 (C, *C*O_2D), 171.8 (4 × C, *C*O_2D), 143.6 (C, arom.), 137.1 (C, arom.), 132.0 (2 × CH, arom.), 131.9 (2 × CH, arom.), 66.2 (CH, N$^+$*C*HCO_2D), 58.0 (4 × CH_2, N$^+$*C*$H_2$$CO_2$D), 56.0 [2 × CH_2, N$^+$(CH_2*C*H_2N$^+$)$_2$], 49.5 [2 × CH_2, N$^+$(*C*$H_2$$CH_2N^+$)$_2$], 43.5 ($CH_2$, *C*$H_2N^+D_3$), 37.1 ($CH_2$, one of $CH_2$$CH_2$$CH_2$$C_6H_4$$CH_2$), 35.2 ($CH_2$, one of $CH_2$$CH_2$$CH_2$$C_6H_4$$CH_2$), 30.5 ($CH_2$, one of $CH_2$$CH_2$$CH_2$$C_6H_4$$CH_2$), 30.2 ($CH_2$, one of $CH_2$$CH_2$$CH_2$$C_6H_4$$CH_2$). ESI-HRMS: *m/z* [M – H]$^-$ calcd for $C_{25}H_{37}N_4O_{10}$: 553.2510; found: 553.2520. Anal. Calcd for $C_{25}H_{38}N_4O_{10}$·$(HCl)_4$·$(H_2O)_{4.5}$: C, 38.42; H, 6.58; N, 7.17. Found: C, 38.32; H, 6.33; N, 7.19..