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Tetra-*n*-butylammonium fluoride: an efficient base for aza-Michael addition—synthesis of glycosyl β-amino acid esters†

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Abstract—A mild and efficient route to glycosyl β-amino acid esters, exploiting the stereoselective Michael addition of benzylamine, in the presence of tetra-*n*-butylammonium fluoride, to sugar derived γ-alkoxy α,β-unsaturated esters is described.
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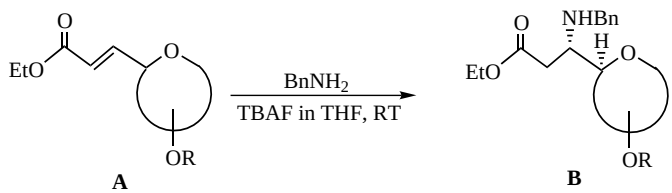
The synthesis of β-amino acids,[1–3] which are constituents of several natural products and useful starting materials for the synthesis of several classes of bioactive compounds, has received much attention in the recent past. β-Peptides,[4,5] the non-natural oligomers of β-amino acids, have been targeted as potential peptidomimetics, since unlike α-amino acid peptides they are stable to peptidases and are more conformationally rigid.[6] The structure can also be tuned by altering the side chain position in the monomer, hence, the synthesis of β-amino acids has attracted much attention. Even though glycosyl α-amino acids are fragments of several natural products,[7] the same is not generally true of glycosyl β-amino acids.

In continuation of our interest in the conversion of monosaccharides into new glyco substances,[8–13] we herein report the development of TBAF as an efficient reagent in the aza-Michael addition for the synthesis of new glycosyl β-amino esters (Eq. (1)).

Of the many methods for the synthesis of β-amino esters, the addition of nitrogen nucleophiles[14–18] to α,β-unsaturated esters is one of the most elegant and flexible. Conjugate addition of chiral amines or amine addition to chiral esters is a well-studied pathway, however, aza-Michael addition onto γ-alkoxy α,β-unsaturated esters[19] is a much less adopted protocol. In the present study of the synthesis of glycosyl β-amino esters through aza-Michael addition, the requisite sugar based Michael acceptors **1**–**4**, **11**–**13** and **20** were prepared from the corresponding sugar aldehydes by Wittig olefination reaction. Treatment of **1** (Scheme 1) with benzylamide (prepared by treatment of $BnNH_2$ with *n*-BuLi) at –40°C in THF for 25 min gave the ester **5**, but in very poor yield (15%), the major product being the amide **6** (Table 1). Similarly, ester **2** under the above reaction conditions gave **7** in 10% yield and the amide **8**. However, the conjugate esters **3** and **4** gave amides **9** and **10** as exclusive products with low yields.

The poor results obtained using benzylamine and *n*-BuLi prompted us to look for a different base to achieve more successful *C–N* bond formation. A literature survey revealed that the fluoride ion[20] in TBAF is a strong base and different from conventional bases in many respects, in particular it requires no special preparation and the use of other strong bases prior to the reaction is not necessary. Hence, TBAF was investigated as an alternative base to enhance the reactivity of the nitrogen nucleophile for the aza-Michael addition.



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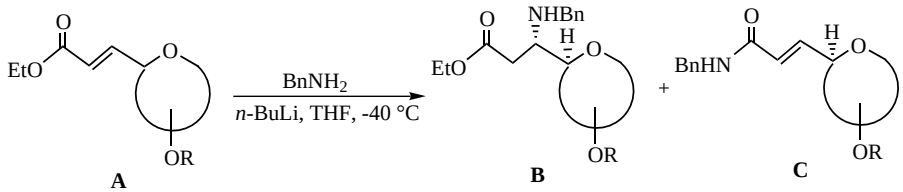
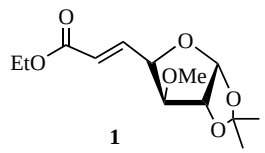
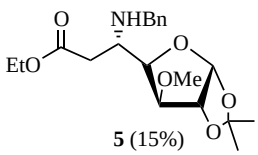
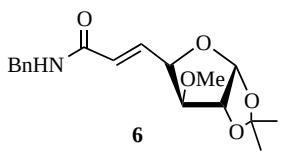
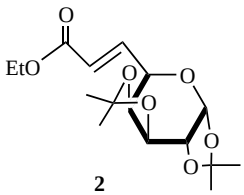
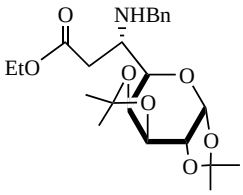
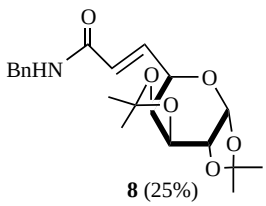
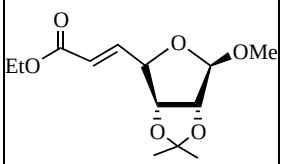
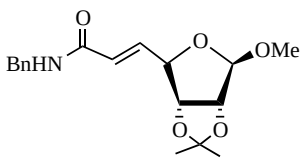
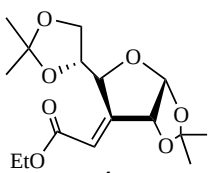
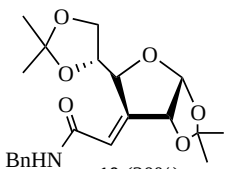


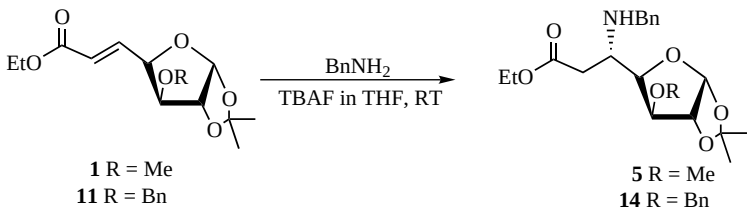
Scheme 1.

Table 1. Michael addition of $BnNH_2$ in the presence of *n*-BuLi at −40°C

Entry	α,β-unsaturated ester	β-amino ester (yield)	Amide (yield)
1	 **1**	 **5** (15%)	 **6**
2	 **2**	 **7** (10%)	 **8** (25%)
3	 **3**	—	 **9** (25%)
4	 **4**	—	 **10** (30%)

Accordingly, the reaction of ester **1** (Scheme 2) with benzylamine in the presence of TBAF (1N solution in THF, 1 equiv.) at room temperature indeed afforded the β-amino ester **5** (75%). The glycosyl β-amino ester **5** was fully characterised by spectral analysis and the diastereomeric excess was ascertained via chiral HPLC analysis. (Chiral-OD column; mobile phase: 15% isopropanol in *n*-hexane.)

The *syn*-stereoselectivity in the TBAF-mediated Michael addition and stereochemical assignment in the present study is in accordance with the literature precedence[21] and was experimentally proven. Accordingly, ester **11** on aza-Michael addition gave **14**[22] (Chiral HPLC, 88.8:6.4) in 68% yield, $[\alpha]_D$ −25.4 (*c* 0.32, $CHCl_3$), which was comparable with the reported[23] value of $[\alpha]_D$ −26.25 (*c* 0.32, $CHCl_3$). Extension of

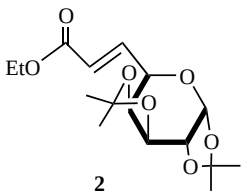
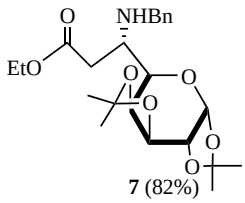
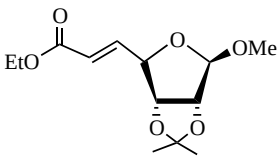
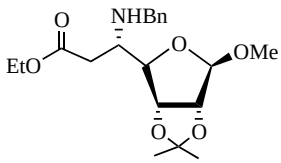
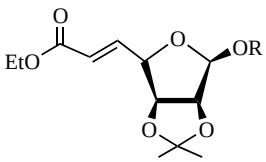
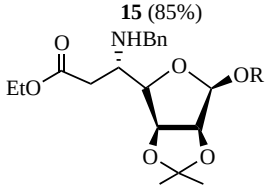


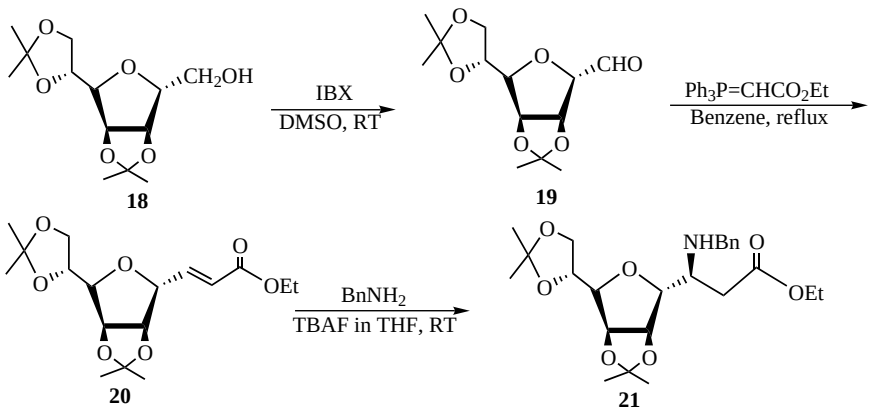
Scheme 2.

TBAF methodology to the Michael acceptors **2**, **3**, **12** and **13** (Table 2) gave the corresponding β-amino esters **7** and **15**–**17**, respectively, in good yields.[24]

Having developed TBAF for the first time as an efficient base for aza-Michael addition and successfully synthesised glycosyl β-amino esters for the first time, the methodology was extended to anomerically linked β-amino esters. Accordingly, the requisite ester **20** (Scheme 3) was prepared from the known alcohol **18**[25] in two steps viz. (a) oxidation of **18** with IBX in DMSO and (b) Wittig olefination of aldehyde **19**. The thus prepared ester **20** on reaction with benzylamine and TBAF in THF at room temperature over 24 h gave the β-amino ester **21** in 70% yield.[26]

Table 2. Michael addition of $BnNH_2$ in the presence of TBAF in THF

Entry	α,β-unsaturated ester	β-amino ester (yield)	time (h.)	d.r. (HPLC)
1	**1**	**5** (75%)	22	92.2 : 5.54
2	**11**	**14** (68%)	24	88.8 : 6.40
3	 **2**	 **7** (82%)	24	93.9 : 2.97
4	 **3**	 **15** (85%)	30	92.63 : 2.82
5	 **12** R = Me **13** R = Bn	 **16** R = Me (80%) **17** R = Bn (75%)	30	89.5 : 7.30 91.45 : 4.89
6	**20**	**21** (70%)	24	93.79 : 3.85



Scheme 3.

Thus, in conclusion the initial drawback of glycosyl β-amino ester synthesis using amides derived from primary amines and *n*-BuLi was successfully countered by the application of TBAF as an efficient base for the aza-Michael addition to synthesize glycosyl β-amino esters for the first time. The main drawback of 1,2-addition with the amides of primary amines is thus solved efficiently by the use of TBAF as an alternative and excellent base. Further, the *syn*-stereoselectivity of the aza-Michael addition was proven unambiguously by comparing the spectral properties of the products with reported data.

Acknowledgements

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References

1. Cole, D. C. *Tetrahedron* **1994**, *50*, 9517–9582.
2. Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichim. Acta* **1994**, *27*, 3–11.
3. Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, 117–128.
4. Daura, X.; Gademann, K.; Juan, B.; Seebach, D.; vanGunsteren, W. F.; Mark, A. E. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 236–240.
5. Chung, Y. J.; Christianson, L. A.; Stanger, H. E.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1998**, *120*, 10555–10556.
6. Gellman, S. H. *Acc. Chem. Res.* **1998**, *2*, 173–180.
7. Burkhart, F.; Hoffmann, M.; Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1191–1192 and references cited therein.
8. Sharma, G. V. M.; Hymavathi, L.; Radhakrishna, P. *Tetrahedron Lett.* **1997**, *38*, 6929–6932.
9. Sharma, G. V. M.; Chander, A. S.; Krishnudu, K.; Radhakrishna, P. *Tetrahedron Lett.* **1997**, *38*, 9051–9054.
10. Sharma, G. V. M.; Chander, A. S.; Krishnudu, K.; Radhakrishna, P. *Tetrahedron Lett.* **1998**, *39*, 6957–6960.
11. Sharma, G. V. M.; Reddy, V. G.; Radhakrishna, P. *Tetrahedron Lett.* **1999**, *40*, 1783–1786.
12. Sharma, G. V. M.; Chander, A. S.; Reddy, V. G.; Krishnudu, K.; Ramana Rao, M. H. V.; Kunwar, A. C. *Tetrahedron Lett.* **2000**, *41*, 1997–2000.
13. Sharma, G. V. M.; Chander, A. S.; Krishnudu, K.; Radhakrishna, P.; Ramana Rao, M. H. V.; Kunwar, A. C. *Tetrahedron: Asymmetry* **2000**, *11*, 2643–2646.
14. Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1991**, *2*, 183–186.
15. Davies, S. G.; Smyth, G. D. *Tetrahedron: Asymmetry* **1996**, *7*, 1273–1274.
16. Enders, D.; Walh, H.; Bettray, W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 455–456.
17. Tsukada, N.; Shimada, T.; Gyoung, Y. S.; Asao, N.; Yamamoto, Y. *J. Org. Chem.* **1995**, *60*, 143–148.
18. Reetz, M. T.; Rohrig, D. *Tetrahedron Lett.* **1994**, *35*, 8765–8768.
19. Asao, N.; Shimada, T.; Sodo, T.; Tsukada, N.; Yawaza, K.; Gyoung, Y. S.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 6274–6282.
20. Clark, J. H. *Chem. Rev.* **1980**, *80*, 429–452.
21. Costa, J. S.; Dias, A. G.; Anholeto, A. L.; Monteiro, M. D.; Patrocinio, V. L.; Costa, R. R. P. *J. Org. Chem.* **1997**, *62*, 4002–4006.
22. Selected data for compound **14**: Mp 69–70°C (lit.[22] mp 70–72°C) $[\alpha]_D=-25.4$ (*c* 0.32, $CHCl_3$) (lit.[22] $[\alpha]_D=-26.25$ (*c* 0.32, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (t, 3H, $J=7.15$ Hz, CH_3), 1.30, 1.47 (2s, 6H, CH_3), 1.87 (brs, 1H, NH), 2.28 (dd, 1H, $J=6.48$, 14.75 Hz, H-6 or 6′), 2.39 (dd, 1H, $J=4.69$, 14.75 Hz, H-6 or 6′), 3.40–3.55 (m, 1H, H-5), 3.78 (d, 1H, $J=12.67$ Hz, N$\underline{CH_2}$Ph), 3.84 (d, 1H, $J=12.71$ Hz, N$\underline{CH_2}$Ph), 3.91 (d, 1H, $J_{3,4}=3.24$ Hz, H-3), 4.07 (q, 2H, $J=7.13$ Hz, OCH_2), 4.20 (dd, 1H, $J_{3,4}=3.27$, $J_{4,5}=8.84$ Hz, H-4), 4.43 (d, 1H, $J=11.81$ Hz, O$\underline{CH_2}$Ph), 4.59 (d, 1H, $J_{1,2}=3.91$ Hz, H-2), 4.68 (d, 1H, $J=11.85$ Hz, O$\underline{CH_2}$Ph), 5.90 (d, 1H, $J_{1,2}=3.89$ Hz, H-1), 7.15–7.36 (m, 10H, Ph); FABMS: 440 (M^+-15); FABHRMS: calcd for $C_{26}H_{32}NO_6$ (M^+-1): 454.222963. Observed: 454.222630.
23. Patil, N. T.; Tilekar, J. N.; Dhavale, D. D. *J. Org. Chem.* **2001**, *66*, 1065–1074.
Compound **14** and its C(5) epimer were prepared by the method reported by Dhavale et al. for comparing the data of **14** prepared in the present study to ascertain the *syn*-selectivity.
24. Selected data for compound **15**: $[\alpha]_D=-20.3$ (*c* 2.8, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.20–1.35 (m, 6H, CH_3), 1.49 (s, 3H, CH_3), 1.85 (br. s, 1H, NH), 2.50–2.60 (m, 2H, H-6,6′), 3.09 (q, 1H, $J=5.4$, 13.6 Hz, H-5), 3.33 (s, 3H, OCH_3), 3.67, 3.89 (2d, 2H, NCH_2Ph), 4.13 (q, 2H, OCH_2), 4.30 (d, 1H, $J_{4,5}=5.2$ Hz, H-4), 4.58 (d, 1H, H-2), 4.70 (d, 1H, $J_{2,3}=4.8$ Hz, H-3), 4.92 (s, 1H, H-1), 7.20–7.40 (m, 5H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 25.0, 26.6, 35.8, 50.7, 55.4, 56.1, 60.1, 82.5, 85.6, 89.0, 110.8, 111.9, 126.7, 127.8 (2C), 128.1 (2C), 140.2, 171.5; FABMS: 380 (M^++1, 100%); FABHRMS: calcd for $C_{20}H_{30}NO_6$ (M^++1): 380.207313. Observed: 380.207503.
Selected data for compound **16**: $[\alpha]_D=+44.5$ (*c* 2.8, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.20–1.40 (m, 6H, CH_3), 1.45 (s, 3H, CH_3), 1.90 (br. s, 1H, NH), 2.55, 2.71 (2dd, 2H, $J=4.6$, 14.5 Hz, H-6,6′), 3.27 (s, 3H, OCH_3), 3.40–3.50 (m, 1H, H-5), 3.87–3.96 (m, 3H, H-4, NCH_2Ph), 4.15 (q, 2H, OCH_2), 4.50 (d, 1H, $J_{2,3}=5.6$ Hz, H-2), 4.76 (dd, 1H, H-3), 4.80 (s, 1H, H-1), 7.20–7.40 (m, 5H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 24.8, 26.0, 35.9, 51.2, 54.0, 54.4, 60.2, 79.7, 81.5, 85.0, 106.8, 112.3, 126.8, 128.1 (2C), 128.2 (2C), 140.1, 171.5; FABMS: 380 (M^++1); FABHRMS: calcd for $C_{20}H_{30}NO_6$ (M^++1): 380.207313. Observed: 380.207510.
25. Frechou, C.; Dheilly, L.; Beaupere, D.; Uzanet, R.; Demailly, G. *Tetrahedron Lett.* **1992**, *33*, 5061–5064.
26. Selected data for compound **21**: $[\alpha]_D=+10.5$ (*c* 0.86, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.20–1.32 (m, 6H, CH_3), 1.35, 1.40, 1.50 (s, 9H, CH_3), 1.80 (br. s, 1H, NH), 2.40–2.60 (m, 2H, CH_2), 2.98 (q, 1H, $J=5.4$, 11.8 Hz, H-7), 3.65, 3.85 (2d, 2H, NCH_2Ph), 3.80 (dd, 1H, H-5), 3.90–4.05 (m, 2H, H-6,6′), 4.13 (q, 2H, OCH_2), 4.28 (q, 2H, H-1, 4), 4.60 (d, 1H, $J_{2,3}=5.7$ Hz, H-2), 5.74 (dd, 1H, H-3), 7.19–7.38 (m, 5H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2, 24.8, 25.3 (2C), 26.3, 26.9, 36.2, 51.5, 54.7, 60.6, 66.7, 73.7, 81.2, 83.6, 87.1, 96.1, 109.0, 112.7, 127.2, 129.2 (2C), 129.5, 139.6, 171.8; FABMS: 450 (M^++1); FABHRMS: calcd for $C_{24}H_{36}NO_7$ (M^++1): 450.249178. Observed: 450.249697.