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One-pot easy conversion of Baylis–Hillman adducts into carbamates of unsaturated β-amino acids

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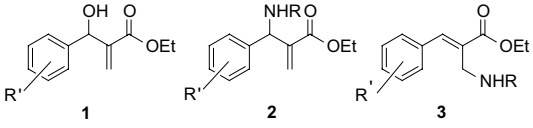
Abstract—An easy, one-pot transformation of Baylis–Hillman adducts into carbamates of unsaturated β-amino acids, for example, 2-(aryl(methoxycarbonylamino)methyl)acrylic acid methyl esters **7** and 2-(methoxycarbonyl aminomethyl)-3-arylacrylic acid methyl esters **8** via reaction with the Burgess reagent is described.

The Baylis–Hillman reaction is a well-known method for coupling aldehydes and activated alkenes and is catalysed by tertiary amines or phosphines.[1] The reaction with methyl acrylate and aromatic aldehydes gives α-methylene-β-hydroxy esters **1**, which have been transformed into various useful compounds. Recently, the Baylis–Hillman reaction has attracted the attention of many synthetic organic chemists because the resulting adducts can be transformed into a variety of natural and unnatural compounds.[2] Several biologically important natural products have been synthesised using this reaction as a key step.[3]

β-Amino acids are an important class of compound due to their applications in medicinal chemistry and their biological activity (e.g., *N*-benzoyl-phenylisoserine: taxol side-chain). They undergo little or no degradation by peptidases. Non-peptidic β-amino acids are found in β-lactam antibiotics, HIV-protease inhibitors and enzyme inhibitors.[4] β-Amino acids can be used in structural biology and as building blocks for the design of new peptidomimetics.[5] However, little attention has been directed towards the conversion of Baylis–Hillman adducts into the corresponding β-amino acids.[6] Recently, the aza version of the reaction, for example, exchanging the aldehyde reactant for an aldimine[7] or iminium salt[8] has been reported. In addition, β-amino acid derivatives **2** can be obtained by a simple substitution reaction on the adducts **1**, displacing the alcohol functionality with an amine.[9]



Recently Orena and co-workers reported that treatment of *N*-*p*-toluenesulfonyl carbamates, prepared from the corresponding Baylis–Hillman adducts, with a catalytic amount of DBU in CH_2Cl_2, gave (*E*)-2-(*p*-toluenesulfonylaminomethyl)propenoates **3** (R = Ts) exclusively.[10]

In order to prepare new, non-proteinogenic amino acids, which can induce conformational restrictions in oligopeptides,[11] the products of the Baylis–Hillman reaction were employed. In this research we developed a convenient procedure for the preparation of unsaturated β-amino acid derivatives using the reaction of the Baylis–Hillman adducts with the Burgess reagent.[12] Methyl *N*-(triethylammoniumsulfonyl) carbamate **4**, also known as the Burgess reagent, is a mild and selective dehydrating agent, and can be successfully utilised for the preparation of alkenes and carbamates from alcohols. This reagent can be prepared from readily available chlorosulfonyl isocyanate and triethylamine in methanol (Scheme 1).[13]

During the course of our studies directed towards the dehydration of alcohols with the Burgess reagent, we found that when the reaction is applied to an allylic

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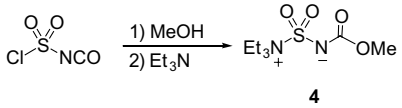


Scheme 1.

alcohol, for example, a Baylis–Hillman adduct, either direct substitution (S_N) or substitution with allylic rearrangement (S_N') ensues, depending upon the experimental conditions, and the corresponding carbamates are formed (Scheme 2).

The first step, that is, the formation of sulfamate ester **6**, takes place in dry THF at 20 °C by interaction of the alcohol **5a**–**g** with the Burgess reagent **4**. When heated to 95 °C, this sulfamate ester undergoes pyrolysis with elimination of SO_3 providing the corresponding carbamates **7a**–**g** in excellent yields.[14,15] This reaction takes place via an S_N pathway and the alcohol moiety is displaced to form the urethane.

When the sulfamate ester **6** was treated with NaH, the corresponding sodium salt was obtained. However, when the sodium salt was decomposed as a solid at 80 °C and the reaction mixture was treated with water, a substitution with an allylic rearrangement occurred to give the carbamates **8a**–**g**.[16,17] A mechanism proposed for this rearrangement is shown in Scheme 3.

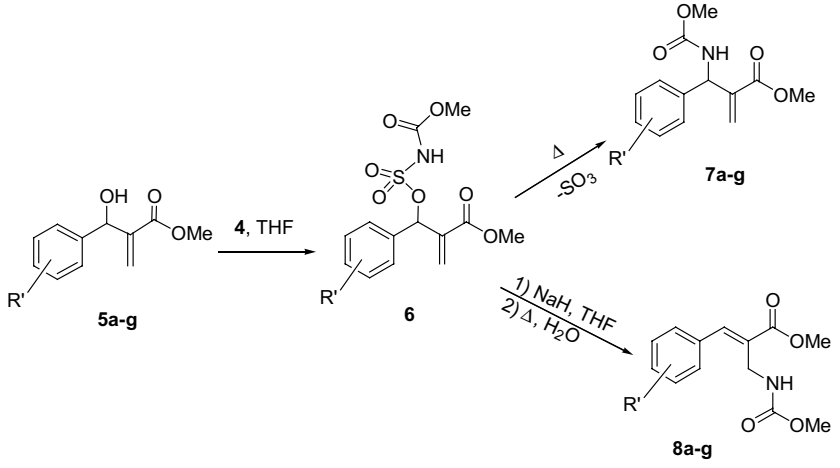
The reactions are clean and the products are obtained in high yields except for the reaction when $R' = NO_2$ (entries **d** and **e**, Table 1). In addition, the reaction conditions are mild so that no side products or decomposition of the products were observed.

In summary, we report that the Burgess reagent can react with Baylis–Hillman adducts to produce sulfamate esters, which can undergo pyrolysis by either direct substitution or substitution with allylic rearrangement, depending upon the experimental conditions, producing carbamates in high yields.

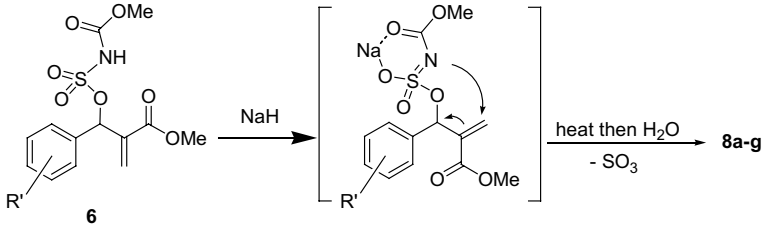
Table 1. Conversion of the Baylis–Hillman adducts into carbamates

Entry	R′	Yield **7** (%)[a,b]	Yield **8** (%)[a,b]
a	H	85[c]	90
b	4-Me	75	87
c	4-OMe	79	88
d	3-NO_2	25	23
e	4-NO_2	20	22
f	4-Cl	88	94
g	2-Cl	86	83

[a] All compounds have been fully characterised spectroscopically by ^{1}H NMR, IR and elemental analyses.
[b] Isolated yields.
[c] Analysed by comparison of its spectroscopic data (^{1}H NMR, IR) with those of an authentic sample (Ref. 10).



Scheme 2.



Scheme 3.

Acknowledgements

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References and notes

1. (a) Langer, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3049–3052; (b) Ciganek, E. *Org. React.* **1997**, *51*, 201–350; (c) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653–4670; (d) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001–8062.
2. Anand, R. V.; Baktharaman, S.; Singh, V. K. *Tetrahedron Lett.* **2002**, *43*, 5393–5395.
3. (a) Mateus, C. R.; Feltrin, M. P.; Costa, A. M.; Coelho, F.; Almeida, N.-P. *Tetrahedron* **2001**, *57*, 6901–6908; (b) Iwabuchi, Y.; Sugihara, T.; Esumi, T.; Hatakeyama, S. *Tetrahedron Lett.* **2001**, *42*, 7867–7871; (c) Iwabuchi, Y.; Furukawa, M.; Esumi, T.; Hatakeyama, S. *Chem. Commun.* **2001**, 2030–2031; (d) Basavaiah, D.; Kumaragurubaran, N.; Sharada, D. S. *Tetrahedron Lett.* **2001**, *42*, 85–87; (e) Paquette, L. A.; Andino, J. M. *Tetrahedron Lett.* **1999**, *40*, 4301–4304; (f) Basavaiah, D.; Pandiaraju, S.; Sarma, P. K. S. *Tetrahedron Lett.* **1994**, *35*, 4227–4230; (g) Buchholz, R.; Hoffmann, H. M. R. *Helv. Chim. Acta* **1991**, *74*, 1213–1219; (h) Weichert, A.; Hoffmann, H. M. R. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2154–2156; (i) Amri, H.; Rambaud, M.; Villieras, J. *Tetrahedron Lett.* **1989**, *30*, 7381–7382.
4. Seebach, D.; Abele, S.; Gademann, K.; Guichard, G.; Hintermann, T.; Jaun, B.; Matthews, J. L.; Schreiber, J. V.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1998**, *81*, 932–939.
5. Seebach, D.; Overhand, M.; Kühnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1996**, *79*, 913–921.
6. (a) Kim, J. N.; Lee, H. J.; Lee, K. Y.; Kim, H. S. *Tetrahedron Lett.* **2001**, *42*, 3737–3740; (b) Kim, J. N.; Kim, H. S.; Gong, J. H.; Chung, Y. M. *Tetrahedron Lett.* **2001**, *42*, 8341–8344.
7. (a) Shi, M.; Xu, Y.-M. *Tetrahedron: Asymmetry* **2002**, *13*, 1195–1200; (b) Aggarwal, V. K.; Martin Castro, A. M.; Mereu, A.; Adams, H. *Tetrahedron Lett.* **2002**, *43*, 1577–1579; (c) Richer, H.; Jung, G. *Tetrahedron Lett.* **1998**, *39*, 2729–2730.
8. Azizi, N.; Saidi, M. R. *Tetrahedron Lett.* **2002**, *43*, 4305–4308.
9. (a) Drewes, S. E.; Horn, M. M.; Ramesar, N. *Synth. Commun.* **2000**, *30*, 1045–1049; (b) Kulkarini, B. A.; Ganesan, A. *J. Comb. Chem.* **1999**, *1*, 373–378; (c) Kundu, M. K.; Bhat, S. V. *Synth. Commun.* **1999**, *29*, 93–99; (d) Nayak, S. K.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1999**, *40*, 981–984; (e) Takagi, M.; Yamamoto, K. *Chem. Lett.* **1989**, 2123–2124; (f) Brown, J. M.; James, A. P.; Prior, L. M. *Tetrahedron Lett.* **1987**, *28*, 2179–2182.
10. Ciclosi, M.; Fava, C.; Galeazzi, R.; Orena, M.; Arques, J. S. *Tetrahedron Lett.* **2002**, *43*, 2199–2202.
11. (a) Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron: Asymmetry* **2001**, *12*, 2731–2741; (b) Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron* **1999**, *55*, 261–270; (c) Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron* **1999**, *55*, 4029–4042; (d) Galeazzi, R.; Geremia, S.; Mobbili, G.; Orena, M. *Tetrahedron: Asymmetry* **1997**, *8*, 133–137; (e) Galeazzi, R.; Geremia, S.; Mobbili, G.; Orena, M. *Tetrahedron: Asymmetry* **1996**, *7*, 3573–3584; (f) Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron* **1996**, *52*, 1069–1084; (g) Galeazzi, R.; Geremia, S.; Mobbili, G.; Orena, M. *Tetrahedron: Asymmetry* **1996**, *7*, 79–88.
12. (a) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26–31; (b) Atkins, G. M., Jr.; Burgess, E. M. *J. Am. Chem. Soc.* **1968**, *90*, 4744–4745.
13. Brain, P.; McIver, E. G. *Tetrahedron Lett.* **2000**, *41*, 831–834.
14. Typical procedure for the preparation of compounds **7a–g**: A solution of alcohol **5a** (5 mmol) in THF (5 mL) was added dropwise to a solution of **4** (6 mmol) in THF (10 mL) in a 50-mL round-bottom flask, fitted with a reflux condenser at 20 °C under an atmosphere of dry nitrogen. After the addition was completed (20 min), the reaction mixture was heated to 95 °C for 60 min. Water (10 mL) was added and the reaction was extracted three times with 10 mL portions of ether. The combined organic layers were dried over $MgSO_4$, and evaporated in vacuo to provide a crude product, which was purified by column chromatography (petroleum ether/diethyl ether 4:1) to give pure isolated **7a** in 85% yield.
15. Selected data for compounds **7b–g**.
7b: Colourless oil, yield 75%; IR (KBr): (ν_{max}/cm^{-1}): 3345 (N–H), 1723 (C=O), 1614 (C=C); Anal. Calcd for $C_{14}H_{17}NO_4$ (Found: C, 63.77; H, 6.45; N, 5.25; requires C, 63.87; H, 6.51; N, 5.32%); ^{1}H NMR (80 MHz, $CDCl_3$): 2.38 (3H, s, CH_3), 3.67 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 5.53 (1H, d, $J = 8.6$), 5.84 (1H, s), 5.87 (1H, d, $J = 8.6$, NH), 6.16 (1H, s), 6.99 (4H, s, ArH) ppm.
7c: Colourless oil, yield 79%; IR (KBr): (ν_{max}/cm^{-1}): 3349 (N–H), 1725 (C=O), 1616 (C=C); Anal. Calcd for $C_{14}H_{17}NO_5$ (Found: C, 60.11; H, 6.25; N, 4.85; requires C, 60.21; H, 6.14; N, 5.02%); ^{1}H NMR (80 MHz, $CDCl_3$): 3.66 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 5.51 (1H, d, $J = 8.8$), 5.82 (1H, s), 5.88 (1H, d, $J = 8.8$, NH), 6.18 (1H, s), 6.71 (2H, d, $J = 8.9$, ArH), 6.99 (2H, d, $J = 8.9$, ArH) ppm.
7d: yellow solid, mp 73–74 °C, yield 25%; IR (KBr): (ν_{max}/cm^{-1}): 3350 (N–H), 1725 (C=O), 1619 (C=C); Anal. Calcd for $C_{13}H_{14}N_2O_6$ (Found: C, 52.99; H, 4.72; N, 9.60; requires C, 53.06; H, 4.80; N, 9.52%); ^{1}H NMR (80 MHz, $CDCl_3$): 3.67 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 5.60 (1H, d, $J = 8.8$), 5.88 (1H, s), 5.89 (1H, d, $J = 8.8$, NH), 6.16 (1H, s), 7.43–8.13 (4H, m, ArH) ppm.
7e: white solid, mp 84–86 °C, yield 20%; IR (KBr): (ν_{max}/cm^{-1}): 3351 (N–H), 1724 (C=O), 1617 (C=C); Anal. Calcd for $C_{13}H_{14}N_2O_6$ (Found: C, 53.00; H, 4.74; N, 9.58; requires C, 53.06; H, 4.80; N, 9.52 %); ^{1}H NMR (80 MHz, $CDCl_3$): 3.6 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 5.55 (1H, d, $J = 8.7$), 5.86 (1H, s), 5.91 (1H, d, $J = 8.7$, NH), 6.18 (1H, s), 7.37 (2H, d, $J = 8.8$, ArH), 8.11 (2H, d, $J = 8.8$, ArH) ppm.
7f: white solid, mp 56–58 °C, yield 88%; IR (KBr): (ν_{max}/cm^{-1}): 3350 (N–H), 1725 (C=O), 1616 (C=C); Anal. Calcd for $C_{13}H_{14}ClNO_4$ (Found: C, 54.94; H, 5.02; N, 4.87; requires C, 55.04; H, 4.97; N, 4.94%); ^{1}H NMR (80 MHz, $CDCl_3$): 3.72 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 5.50 (1H, d, $J = 8.6$), 5.68 (1H, d, $J = 8.6$, NH), 5.82 (1H, s), 6.24 (1H, s), 7.10 (2H, d, $J = 8.7$, ArH), 7.20 (2H, d, $J = 8.7$, ArH) ppm.
7g: white solid, mp 44–45 ° C, yield 86%; IR (KBr): (ν_{max}/cm^{-1}): 3349 (N–H), 1726 (C=O), 1617 (C=C); Anal. Calcd $C_{13}H_{14}ClNO_4$ (Found: C, 54.96; H, 5.00; N, 4.88; requires C, 55.04; H, 4.97; N, 4.94 %); ^{1}H NMR (80 MHz, $CDCl_3$): 3.68 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 5.60 (1H, d, $J = 8.7$), 5.66 (1H, d, $J = 8.7$, NH), 5.87 (1H, s), 6.29 (1H, s), 6.99–7.22 (4H, m, ArH) ppm.
16. Typical procedure for the preparation of compounds **8a–g**: A solution of alcohol **5a** (5 mmol) in THF (5 mL) was added dropwise to a solution of **4** (6 mmol) in THF

(10 mL) in a 50-mL round-bottom flask, fitted with a reflux condenser at 20 °C under an atmosphere of dry nitrogen. After the addition was completed (20 min), the reaction mixture was treated with sodium hydride (0.12 g, 5 mmol, prepared from 0.22 g of sodium hydride dispersion in mineral oil (60%) by several washings with dry hexane) and the mixture was maintained at ambient temperature until hydrogen evolution had ceased. The solvent was removed under reduced pressure to afford a white solid, which was heated to 80 °C for 30 min. Water (5 mL) was added and the reaction mixture was extracted three times with 10 mL portions of ether. The combined organic layers were dried over $MgSO_4$, and evaporated in vacuo to provide a crude product, which was purified by column chromatography (petroleum ether/diethyl ether 5:1) to give pure isolated **8a** in 90% yield.

17. Selected data for compounds **8a–g**.

8a: Colourless oil, yield 90%; IR (KBr): (ν_{max}/cm^{-1}): 3338 (N–H), 1710 (C=O), 1611 (C=C); Anal. Calcd for $C_{13}H_{15}NO_4$ (Found: C, 62.71; H, 6.01; N, 5.55; requires C, 62.64; H, 6.07; N, 5.62 %); ^{1}H NMR (80 MHz, $CDCl_3$): 3.60 (2H, d, $J = 6.5$), 3.69 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 5.83 (1H, t, $J = 6.5$, NH), 7.16–7.35 (5H, m, ArH), 7.65 (1H, s) ppm.

8b: Colourless oil, yield 87%; IR (KBr): (ν_{max}/cm^{-1}): 3335 (N–H), 1715 (C=O), 1613 (C=C); Anal. Calcd for $C_{14}H_{17}NO_4$ (Found: C, 63.79; H, 6.55; N, 5.25; requires C, 63.87; H, 6.51; N, 5.32 %); ^{1}H NMR (80 MHz, $CDCl_3$): 2.38 (3H, s, CH_3), 3.66 (2H, d, $J = 6.4$), 3.67 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 5.91 (1H, t, $J = 6.4$, NH), 7.10 (2H, d, $J = 8.8$, ArH), 7.23 (2H, d, $J = 8.8$, ArH), 7.62 (1H, s) ppm.

8c: Colourless oil, yield 88%; IR (KBr): (ν_{max}/cm^{-1}): 3340 (N–H), 1715 (C=O), 1613 (C=C); Anal. Calcd for $C_{14}H_{17}NO_5$ (Found: C, 60.17; H, 6.19; N, 4.92; requires C, 60.21; H, 6.14; N, 5.02 %); ^{1}H NMR (80 MHz, $CDCl_3$): 3.60 (3H, s, OCH_3), 3.65 (2H, d, $J = 6.3$), 3.69 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 6.02 (1H, t, $J = 6.3$, NH), 6.77 (2H, d, $J = 8.7$, ArH), 7.2 (2H, d, $J = 8.7$, ArH), 7.60 (1H, s) ppm.

8d: yellow solid, mp 91–93 °C, yield 23%; IR (KBr): (ν_{max}/cm^{-1}): 3357 (N–H), 1720 (C=O), 1616 (C=C); Anal. Calcd for $C_{13}H_{14}N_2O_6$ (Found: C, 52.96; H, 4.74; N, 9.50; requires C, 53.06; H, 4.80; N, 9.52 %); ^{1}H NMR (80 MHz, $CDCl_3$): 3.65 (2H, d, $J = 6.6$), 3.69 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 5.99 (1H, t, $J = 6.6$, NH), 7.03–8.28 (5H, m) ppm.

8e: white solid, mp 91–93 °C, yield 22%; IR (KBr): (ν_{max}/cm^{-1}): 3360 (N–H), 1719 (C=O), 1616 (C=C); Anal. Calcd for $C_{13}H_{14}N_2O_6$ (Found: C, 53.11; H, 4.72; N, 9.50; requires C, 53.06; H, 4.80; N, 9.52 %); ^{1}H NMR (80 MHz, $CDCl_3$): 3.70 (3H, s, OCH_3), 3.76 (2H, d, $J = 6.6$), 3.80 (3H, s, OCH_3), 6.12 (1H, t, $J = 6.6$, NH), 7.59 (2H, d, $J = 8.8$, ArH), 8.19 (2H, d, $J = 8.8$, ArH), 7.75 (1H, s) ppm.

8f: white solid, mp 69–71 °C, yield 94%; IR (KBr): (ν_{max}/cm^{-1}): 3357 (N–H), 1718 (C=O), 1615 (C=C); Anal. Calcd for $C_{13}H_{14}ClNO_4$ (Found: C, 54.98; H, 5.01; N, 4.87; requires C, 55.04; H, 4.97; N, 4.94%); ^{1}H NMR (80 MHz, $CDCl_3$): 3.67 (2H, d, $J = 6.4$), 3.72 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 5.73 (1H, t, $J = 6.4$, NH), 7.20 (2H, d, $J = 8.7$, ArH), 7.29 (2H, d, $J = 8.7$, ArH), 7.59 (1H, s) ppm.

8g: white solid, mp 63–64.5 °C, yield 83%; IR (KBr): (ν_{max}/cm^{-1}): 3349 (N–H), 1720 (C=O), 1617 (C=C); Anal. Calcd $C_{13}H_{14}ClNO_4$ (Found: C, 54.99; H, 5.02; N, 4.83; requires C, 55.04; H, 4.97; N, 4.94 %); ^{1}H NMR (80 MHz, $CDCl_3$): 3.66 (2H, d, $J = 6.6$), 3.68 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 5.69 (1H, t, $J = 6.6$, NH), 7.11–7.30 (4H, m, ArH), 7.79 (1H, s) ppm.