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Highly Efficient Deprotection of *N*-*p*-Toluenesulfinyl Group of β-Branched Baylis–Hillman Adducts by Using Amberlite IR-120 (Plus) Ion-Exchange Resin

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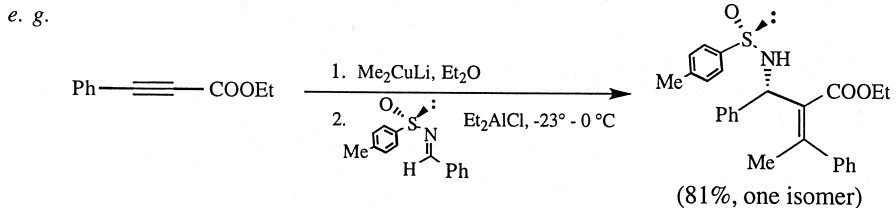
Abstract—An efficient deprotection of *N*-*p*-toluenesulfinyl group of β-branched Baylis–Hillman adducts has been developed by using Amberlite IR-120 (plus) ion-exchange resin in methanol solution at room temperature. Good to quantitative yields have been obtained for six examples. No racemization was detected under the mild conditions. This new method provides a simultaneous deprotection/purification, which has the great advantage over the solution phase deprotection technique of simplicity of work-up.

Enantiopure sulfinimines (thiooxime *S*-oxides)[1] have been utilized as versatile building blocks to react with various anionic species for the asymmetric synthesis of many important compounds such as amines,[2] α- and β-amino acids,[3] α- and β-amino phosphonates,[4] *N*-sulfinyl *cis*-aziridine 2-carboxylic acids,[5] etc. Recently, we reported a new method for the asymmetric Baylis–Hillman adducts, β-alkyl α-(aminoalkyl)acrylates, by reacting enantiopure *p*-toluenesulfinimines with functionalized lithium (α-carbalkoxyvinyl)cuprates.[6] This reaction was conducted by using excess amount of Et_2AlCl as the Lewis acidic promoter in diethyl ether solution (Scheme 1). Since some *p*-toluenesulfinimines, such as (*S*)-(+)-*p*-chlorobenzylidene-*p*-toluenesulfinamide and (*S*)-(+)-*p*-fluorobenzylidene-*p*-toluenesulfinamide, are insoluble in diethyl ether at low temperature, we therefore developed the Et_2O–CH_2Cl_2 cosolvent system for this process by using ytterbium (III) triflate as the catalyst.[7] The scope of this reaction has been extended by allowing those *p*-toluenesulfinimines with low solubility in Et_2O to react with anionic (α-carbalkoxyvinyl)cuprates.



Scheme 1.

The removal of the *N*-*p*-toluenesulfinyl protecting group from the resulting β-monosubstituted and β,β-disubstituted alkyl α-(aminoalkyl)acrylates is necessary to generate free α-alkylidene β-amino acid esters, which are very useful for the synthesis of β-lactam antibiotics, peptidomimetics, β-peptide oligomers and many other biologically important molecules.[8,9] It has been shown that *N*-*p*-toluenesulfinyl and *N*-butanesulfinyl groups can be removed by using CF_3COOH or HCl in methanol or other solvents.[3b–d,10] It seems more convenient to find a mild and cheap polymer resin-based technique to perform this deprotection. More importantly, this technique can allow a simultaneous separation by absorbing the amine salt product onto the polymer resin and direct formation of free amino acid esters. Ion-exchange chromatography has been previously used to expedite the purification of libraries of amines and their derivatives.[11,12] Very recently, Bergbreiter and Romo established a simultaneous deprotection and purification of *N*-Boc amine compounds by using a strongly acidic

Keywords: Baylis–Hillman adducts; *N*-*p*-toluenesulfinyl cleavage; Amberlite IR-120 (plus) resin.

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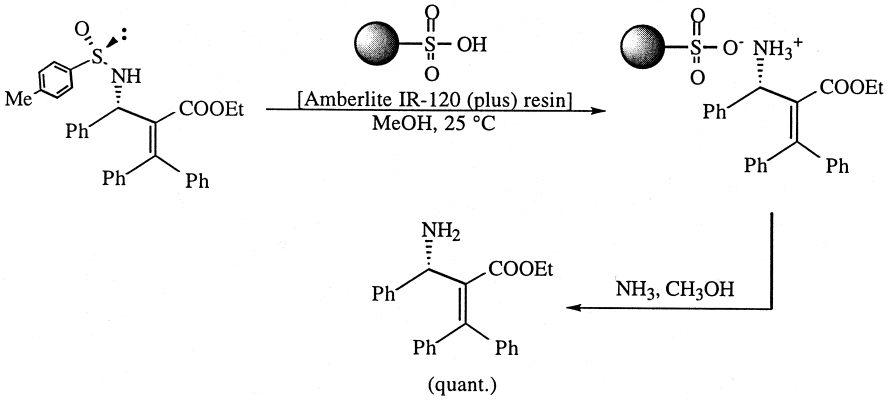
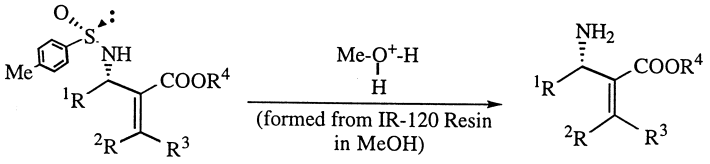


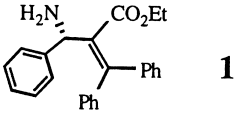
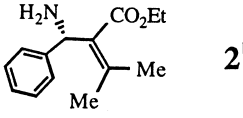
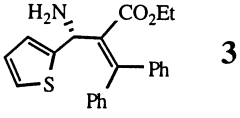
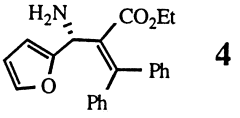
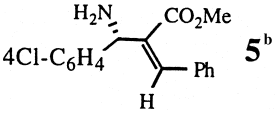
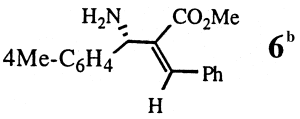
Scheme 2.

Amberlyst 15 ion-exchange resin with great success.[13] Herein, we would like to report an alternative method for a 'one-pot' deprotection/purification of *N*-*p*-toluenesulfinyl α-(aminoalkyl)acrylates by the use of Amberlite IR-120 (plus) ion exchange resin[14] (Scheme 2).

At first, we applied the *N*-Boc cleavage procedure of Bergbreiter and Romo for the *N*-*p*-toluenesulfinyl deprotection but without success. Only a trace amount of the desired free amino esters were generated in the several cases we examined. Therefore, we turned our attention to the use of

Table 1. Results of cleavage of *N*-*p*-toluenesulfinyl group of β-substituted α-(aminoalkyl)acrylates



R^1	R^2	R^3	R^4	Product[a]	Yield (%)
Ph	Ph	Ph	Et	 **1**	Quant.
Ph	Me	Me	Et	 **2**[b]	95
	Ph	Ph	Et	 **3**	84
	Ph	Ph	Et	 **4**	95
4-Cl–C_6H_4–	H	Ph	Me	 **5**[b]	Quant.
4-Me–C_6H_4–	H	Ph	Me	 **6**[b]	96

[a] All of the products are glassy solids or oils.
[b] The reaction started from a non-optically pure substrate.

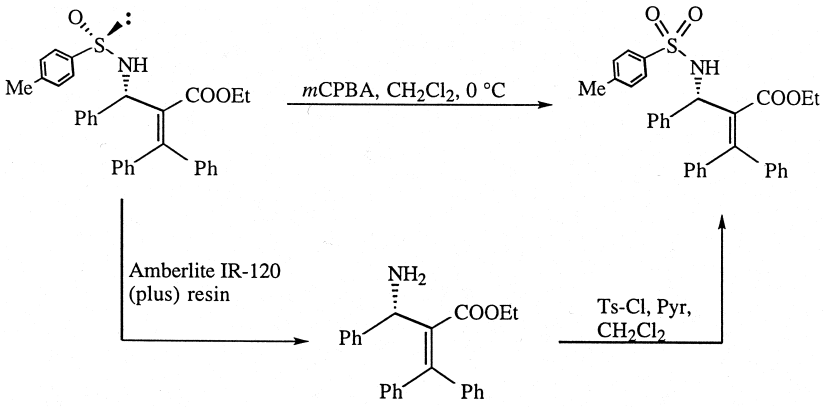
Amberlite IR-120 (plus) ion exchange resin, which is also strongly acidic and much less expensive.[14] Amberlite IR-120 (plus) ion exchange resin has been widely used in ion-exchange chromatography for purifying free amino acid derivatives, even though it has not yet been applied to functional group deprotection. It has been found that *N*-Boc amine deprotection using the Amberlyst IR-15 resin could not proceed smoothly in methanol, but worked very efficiently in dichloromethane, THF and chloroform.[13] However, in the present *N*-*p*-toluenesulfinyl deprotection system, the opposite phenomenon was observed, i.e. the combination of the Amberlite IR-120 (plus) ion exchange resin with the latter three solvents did not drive the deprotection, but with alcohols, resulted in efficient deprotection, methanol working best. The deprotection went to completion by gently stirring the methanol solution of *N*-*p*-toluenesulfinyl α-(aminoalkyl)acrylates with the Amberlite IR-120 (plus) ion exchange resin at room temperature for 12 h. The process was monitored by TLC or crude ^{1}H NMR determination. The amine salt products were completely absorbed onto the Amberlite IR-120 (plus) resin after the cleavage was finished as confirmed by TLC examination of the methanol solution. The resin and bound product were separated simply by filtration. The free amino esters were obtained finally by treating the resin with excess ammonia solution. As shown in Table 1, quantitative or excellent yields were obtained for the cleavage of both β-monosubstituted and β,β-disubstituted alkyl α-(aminoalkyl)acrylates (**1**–**2**, **4**–**6**); only in one case (**3**) was obtained a slightly lower yield (84%).

We believe that this new *N*-*p*-toluenesulfinyl deprotection could be conducted mainly by acidic methoxonium ions instead of the Amberlite IR-120 resin itself. The methoxonium ions could be formed through the transfer of a proton from the $-SO_3H$ group on the resin to methanol oxygen atom. This hypothesis is supported by the fact this cleavage did not proceed in several other aprotic solvents as mentioned before. To further confirm this, the cleavage reaction was also performed by dissolving the *N*-*p*-toluenesulfinyl-α-(aminoalkyl)acrylates in a small amount of methanol and absorbing them on Amberlite IR-120 (plus) resin in a column. Incomplete deprotection was observed probably because methoxonium ions cannot contact effectively the substrate molecules and also more methoxonium ions are needed for efficient deprotection. In addition, the smaller amount of methanol caused solubility problems when highly hydrophobic *N*-*p*-toluenesulfinyl-α-(aminoalkyl)acrylates, e.g. β,β-diphenyl-α-(aminoalkyl)acrylates were employed as the cleavage substrates. After the cleavage reaction, methyl-*p*-toluenesulfinate is presumably generated, which is similar to the sulfinimine regeneration process where menthol was employed in the presence of a strong acid.[3c]

Neither racemization nor side-products from amine addition to the α,β-unsaturated adduct were observed under the present new conditions. The former was confirmed by chemical conversions (Scheme 3). The single isomer of *N*-*p*-toluenesulfonyl β,β-diphenyl-α-(aminoalkyl)acrylate was synthesized via the oxidation reaction of its *N*-*p*-toluenesulfinyl precursor by using *m*CPBA in CH_2Cl_2 at 0°C. This product was confirmed to be optically pure by HPLC measurement using two types of chiralcel columns [chiralcel OD-H, *i*-PrOH/Hexane (15/85, v/v), 0.6 mL min^{-1}, 9.84 min; chiralcel AD, *i*-PrOH/Hexane (15/85, v/v), 0.7 mL min^{-1}, 11.0 min]. Concurrently, β,β-diphenyl-α-(aminoalkyl)acrylate, the cleavage product, was converted into the same compound by treating with toluenesulfonyl chloride in the presence of pyridine in dichloromethane. The product from the latter procedure was proven to be optically pure and identical to the product of the *m*CPBA oxidation using the same HPLC measurement.

After we succeeded in *N*-*p*-toluenesulfinyl deprotection, we also tried the Amberlite IR-120 (plus) resin-methanol system for the cleavage of the *N*-Boc group but without success. Essentially, no deprotection product was observed when the reaction was performed at room temperature for over 24 h.

In summary, the Amberlite IR-120 (plus) ion-exchange resin-methanol combination has been found to efficiently cleave *N*-*p*-toluenesulfinyl group of β-substituted Baylis–Hillman adducts, β-monosubstituted and β,β-disubstituted *N*-(*p*-toluenesulfinyl)-α-(aminoalkyl)acrylates. The polymeric resin-mediated simultaneous deprotection and purification have the great advantage over the solution phase deprotection technique of simplicity of work-up. The resulting free α-alkylidene β-amino esters are very useful for the design and synthesis of many chemically and biologically important compounds.



Scheme 3.

Experimental

General methods

All reactions were conducted at room temperature in vials of appropriate size with magnetic stirring. Dichloromethane was dried and freshly distilled from calcium hydride under nitrogen. Methanol was reagent grade and used without purification. Other commercial chemicals were used without purification and their stoichiometrics were calculated based on the reported purities from the manufacturers. Flash chromatography was performed on E. Merck silica gel 60 (230–400 mesh). ^{1}H NMR spectra were recorded on a Bruker 200 or 300 MHz NMR spectrometers. ^{13}C NMR spectra were recorded at 75 MHz using DMSO-d_6 as the solvent and internal reference. HPLC was performed using a Perkin–Elmer Series 200 HPLC system equipped with a Diode Array detector. Optical rotations were measured using an Autopol III polarimeter (Rudolph Research, Fairfield, NJ). High-resolution mass spectral analysis was conducted by the mass spectroscopy laboratory of the Scripps Research Institute.

Typical deprotection procedure

Into a clean dry vial was loaded the *N*-*p*-toluenesulfinyl-β,β-diphenyl-α-(aminoalkyl)acrylate (50 mg, 0.10 mmol) and methanol (5.0 mL). Into this solution was added Amberlite IR-120 (plus) ion-exchange resin (0.50 g) in one portion. The resulting heterogeneous mixture was stirred in the capped vial at room temperature for 12 h without argon protection. TLC (EtOAc/hexane, 1/2, v/v) showed complete disappearance of the starting material in methanol solution. The Amberlite resin, which absorbed the deprotection product, was separated by suction filtration and then washed with 5.0 mL of methanol. No product was detected in the methanol. The free amino ester was released from the resin by immersing the loaded resin in 15% NH_4OH in methanol (10 mL) overnight. The resin was filtered off and further washed with dilute aqueous ammonia. The combined filtrates were concentrated to dryness to give product **1** (36.0 mg, quant.) as a light yellow oil. $[\alpha]_D^{25}=-263.8$ (*c*, 0.37, 95% EtOH); ^{1}H NMR (200 MHz, DMSO-d_6): 7.24–7.10 (m, 15H), 4.79 (s, 1H), 3.68 (q, J=7.60 Hz, 2H), 0.63 (t, J=7.15 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.2, 145.8, 142.1, 139.9, 135.6, 128.6, 128.1, 128.0, 127.8, 127.7, 126.7, 126.2, 125.5, 59.8, 55.0, 13.2; HRMS (FAB) *m*/*z* (M^++1) found 358.1819, calcd for $C_{24}H_{23}O_2N$ 358.1807.

2. Light yellow oil (36.6 mg, 95% yield); ^{1}H NMR (200 MHz, DMSO-d_6): 7.36–7.15 (m, 5H), 4.91 (s, 1H), 3.92 (q, J=7.60 Hz, 2H), 1.81 (s, 6H), 0.98 (t, J=7.11 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.3, 144.7, 137.5, 133.3, 127.8, 126.4, 126.1, 59.4, 53.6, 22.7, 20.5, 13.9; HRMS (FAB) *m*/*z* (M^++1) found 234.1484, calcd for $C_{14}H_{19}O_2N$ 234.1495.

3. Light yellow oil (30.9 mg, 84% yield); $[\alpha]_D^{25}=-266.7$ (*c*, 0.26, 95% EtOH); ^{1}H NMR (200 MHz, DMSO-d_6): 7.43–6.90 (m, 13H), 4.84 (s, 1H), 3.72 (q, J=7.10 Hz, 2H), 0.65 (t, J=7.10 Hz 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.3, 148.9, 145.9, 141.8, 139.7, 135.6, 128.7, 128.6, 128.2, 128.1, 127.8, 126.8, 124.6, 123.1, 59.8, 52.8, 13.2; HRMS (FAB) *m*/*z* (M+Na) found 386.1181, calcd for $C_{22}H_{21}O_3NNa$ 386.1191.

4. Light yellow oil (39.6 mg, 95% yield); $[\alpha]_D^{25}=-282.6$ (*c*, 0.31, 95% EtOH); ^{1}H NMR (200 MHz, DMSO-d_6): 7.54–7.07 (m, 11H), 6.36 (m, 1H), 6.24 (m, 1H) 4.72 (s, 1H) 3.73 (q, J=7.04 Hz, 2H), 0.69 (t, J=7.08 Hz 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.2, 156.6, 145.3, 141.8, 141.6, 139.6, 134.4, 128.9, 128.5, 128.2, 128.0, 127.9, 127.7, 110.3, 105.4, 59.8, 51.0, 13.3; HRMS (FAB) *m*/*z* (M+Na) found 370.1412, calcd for $C_{22}H_{21}O_3NNa$ 370.1419.

5. Light yellow oil (45.2 mg, quant.); ^{1}H NMR (200 MHz, DMSO-d_6): 7.31–7.19 (m, 9H), 6.92 (s, 1H), 4.83 (s, 1H), 3.46 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.1, 142.4, 138.4, 135.4, 131.5, 130.6, 129.0, 128.4, 128.1, 128.0, 58.0, 51.4; HRMS (FAB) *m*/*z* (M^++1) found 302.0958, calcd for $C_{17}H_{17}O_2NCl$ 302.0948.

6. Light yellow oil (33.8 mg, 96% yield); ^{1}H NMR (200 MHz, DMSO-d_6): 7.33–7.09 (m, 9H), 6.88 (s, 1H), 4.79 (s, 1H), 3.44 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.3, 140.3, 139.1, 136.0, 135.6, 130.0, 128.7, 128.3, 127.9, 127.8, 127.0, 58.3, 51.3, 20.7; HRMS (FAB) *m*/*z* (M^++1) found 282.1499, calcd for $C_{18}H_{20}O_2N$ 282.1494.

Acknowledgements

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References

1. (a) Davis, F. A.; Zhou, P.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13. (b) Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1403. (c) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278.

2. (a) Liu, G.-C.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913. (b) Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 268. (c) Hua, D. H.; Miao, S. W.; Chen, J. S.; Iguchi, S. *J. Org. Chem.* **1991**, *56*, 5. (d) Moreau, P.; Essiz, M.; Merour, J.-Y.; Bouzard, D. *Tetrahedron: Asymmetry* **1997**, *8*, 591. (e) Hose, D. R. J.; Mahon, M. F.; Molloy, K. C.; Raynham, T.; Willis, M. *J. Chem. Soc., Perkin Trans. 1*, **1996**, 691.

3. (a) Davis, F. A.; Fanelli, D. L. *J. Org. Chem.* **1998**, *63*, 1981. (b) Davis, F. A.; Portonovo, P. S.; Reddy, R. E.; Chiu, Y.-H. *J. Org. Chem.* **1996**, *61*, 440. (c) Davis, F. A.; Szewczyk, J. M.; Reddy, G. V. *J. Org. Chem.* **1995**, *60*, 7037. (d) Hua, D. H.; Lagneau, N.; Wang, H.; Chen, J. *Tetrahedron: Asymmetry* **1995**, *6*, 349. (e) Davis, F. A.; Szewczyk, J. M. *Tetrahedron Lett.* **1998**, *39*, 5951. (f) Bravo, P.; Crucianelli, M.; Vergani, B.; Zanda, M. *Tetrahedron Lett.* **1998**, *39*, 7771.

4. (a) Davis, F. A.; McCoull, W. *Tetrahedron Lett.* **1999**, *40*, 249. (b) Lefebvre, I. M.; Evans, S. A., Jr. *J. Org. Chem.* **1997**, *62*, 7532. (c) Mikolajczyk, M.; Lyzwa, P.; Drabowicz, J.; Wieczorek, M. W.;

Blaszczyk, J. *J. Chem. Soc. Commun.* **1996**, 1503; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1994**, *64*, 12.
5. (a) Davis, F. A.; Reddy, G. V.; Liu, H. *J. Am. Chem. Soc.* **1995**, *117*, 3651. (b) Davis, F. A.; Reddy, G. V.; Liang, C.-H. *Tetrahedron Lett.* **1997**, *38*, 5139. (c) Davis, F. A.; Liang, C.-H.; Liu, H. *J. Org. Chem.* **1997**, *62*, 3796. (d) Ruano, J. L.; Fernandez, I.; Catalina, M.; Cruz, A. A. *Tetrahedron: Asymmetry* **1996**, *7*, 3407.
6. (a) Li, G.; Wei, H.-X.; Whittlesey, B. R.; Batrice, N. N. *J. Org. Chem.* **1999**, *64*, 1061. (b) Wei, H.-X.; Hook, J. D.; Fitzgerald, K. A.; Li, G. *Tetrahedron: Asymmetry* **1999**, *10*, 661.
7. Li, G.; Wei, H.-X.; Hook, J. D. *Tetrahedron Lett.* **1999**, *40*, 4611.
8. (a) Matthews, J. L.; Braun, C.; Guibourdenche, C.; Overhand, M.; Seebach, D. In *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley: New York, 1996, pp 105–126. (b) Gademann, K.; Ernst, M.; Hoyer, D.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1223.
9. (a) Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichimica Acta* **1994**, *27*, 3. (b) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517.
10. Ruano, J. L. G.; Fernandez, I.; Catalina, M. del P.; Hermoso, J. A.; Sanz-Aparicio, J.; Martinez-Repoll, M. *J. Org. Chem.* **1998**, *63*, 7157.
11. (a) Brown, S. D.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 6331. (b) Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 2574.
12. Siegel, M. G.; Hahn, P. J.; Dressman, B. A.; Fritz, J. E.; Grunwell, J. R.; Kaldor, S. W. *Tetrahedron Lett.* **1997**, *38*, 3357.
13. Liu, Y. -S.; Zhao, C.; Bergbreiter, D. E.; Romo, D. *J. Org. Chem.* **1998**, *63*, 3471.
14. The current Aldrich prices of the two resins are: Amberlyst IR-15 resin, $164.55/2.0 kg; Amberlite IR-120 (plus) resin, $65.40/4.0 kg.