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Facile preparation of N-protected 2-alkylidene-1,3-imidazolidines

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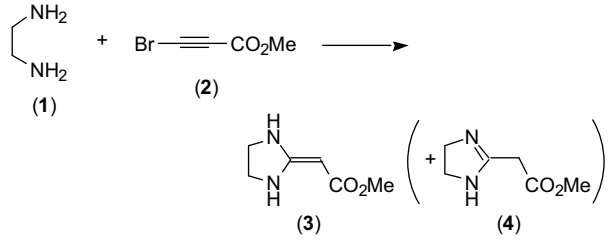
Abstract

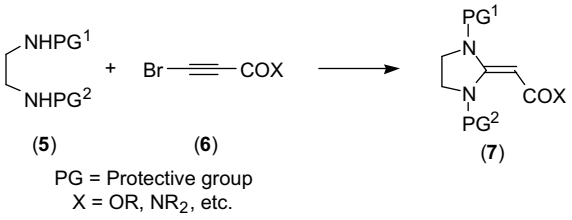
Stereoselective preparation of unsymmetrically protected 2-alkylidene-1,3-imidazolidines was achieved by the reaction of N,N′-protected ethylenediamine, bromopropynamide, and K_3PO_4 in hot DMF. When N-protected aminoethanol was used in place of the protected ethylenediamine, an oxazolidine derivative was produced.

Keywords: Imidazolidine; Oxazolidine; Bromoacetylene; Sulfonamide

Alkylideneimidazolidines of structure **3**[1] are conveniently prepared by the conjugate addition of 1,2-diamines **1** to bromopropiolic acid derivatives such as **2** as shown in Scheme 1, while preventing the formation of the tautomeric isomer **4**.[2] As the compounds represented by **3** have active hydrogens on the nitrogen atoms, their N-protection is often required to prevent complications in further synthetic transformations.[3] However, their efficient and full protection is rarely documented.[4] A critical issue in selective protection is to discriminate between the two amine moieties cis and trans to the carbonyl group. Here we report that a suitably protected diamine **5** can be used instead of the amine **1** itself for the direct preparation of the protected



Scheme 1.



Scheme 2.

imidazolidines **7**, even for that of unsymmetrically protected ones, as formulated in Scheme 2. This method has an additional advantage that the product is free from contamination with its double-bond regioisomer, as shown in Scheme 1.

In the above transformation, whether a bis-protected diamine **5** shows sufficient nucleophilicity to the bromopropiolic acid derivative **6** appears to be a serious problem, because protection of an amine usually decreases its nucleophilicity and also retards its reactivity as a result of steric hindrance of the protective group(s). We were discouraged by the fact that the reaction of *N*,*N*′-diacetyl-1,2-ethylenediamine (**8**) and ethyl bromopropiolate or *N*,*N*-diethylbromopropynamide (**9**) (see Table 1, entry 1) did not give the desired product. However, we soon realized the importance of the nature of the protecting group on the diamine

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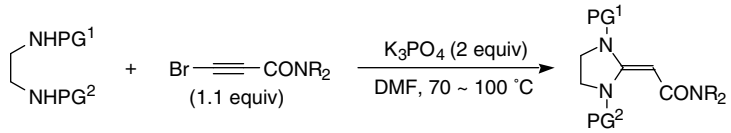
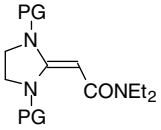
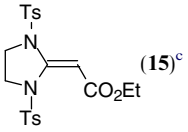
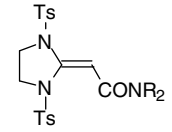
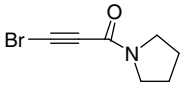
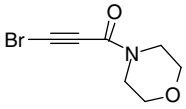
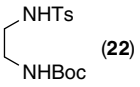
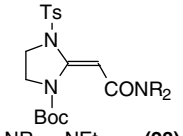
Table 1
Preparation of 2-alkylidene-1,3-imidazolidines[a]



Entry	Diamine	Bromopropynamide	Temperature (°C)	Period (h)	Product	Isolated yield[b] (%)
						
1	PG = Ac (**8**)	Br—≡—$CONEt_2$ (**9**)	100	7	PG = Ac	(0)
2	Boc	**9**	100	7	Boc	(5)
3	Ms	**9**	100	7	Ms	(19)
4	Tf (**10**)	**9**	100	7	Tf (**11**)	33
5	Ts (**12**)	**9**	100	0.5	Ts (**13**)	69
6	Ts (**12**)	**9**	100	7	Ts (**13**)	70
7	**12**	Br—≡—CO_2Et (**14**)	100	7	 (**15**)[c]	44
8	**12**	Br—≡—$CONBn_2$ (**16**)	100	7	 $NR_2 = NBn_2$ (**19**)	85[d]
9	**12**	 (**17**)	100	7	 (**20**)	91
10	**12**	 (**18**)	100	7	 (**21**)	82[e]
11	 (**22**)	**9**	70	0.5	 $NR_2 = NEt_2$ (**23**)	68[f]
12	**22**	**16**	70	0.5	NBn_2 (**24**)	66
13	**22**	**17**	70	5	 (**25**)	60
14	**22**	**18**	70	5	 (**26**)	63

[a] Abbreviations: DMF = *N*,*N*-dimethylformamide, Ac = acetyl, Boc = *t*-butyloxycarbonyl, Ms = methanesufonyl, Tf = trifluoromethanesulfonyl, Ts = *p*-toluenesulfonyl (tosyl), Bn = benzyl.
[b] Yields determined by ^1H NMR are in parentheses.
[c] For structural determination, see Ref. 5.
[d] **16** (2.0 equiv) was used.
[e] **18** (1.0 equiv) was used.
[f] For the *E* stereochemistry of the olefin, see the text.

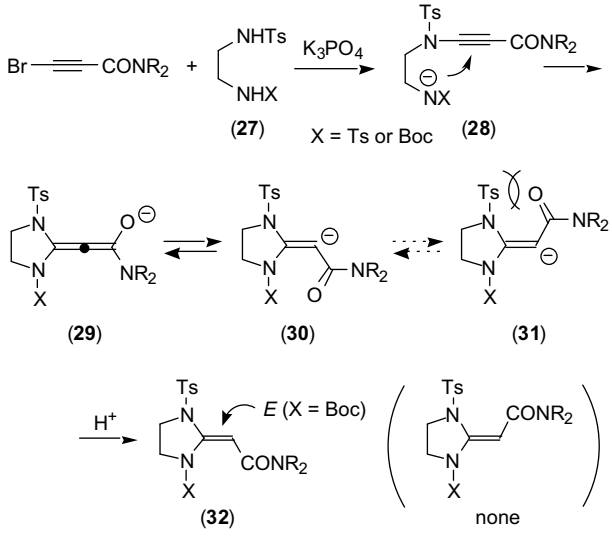
(entries 1–6) and we determined that bis-tosyl-protected diamine **12** is the substrate of choice for the transformation of Scheme 2 (entry 6).[6] Other optimized reaction conditions are the use of K_3PO_4 and DMF as the base and solvent,

respectively (see the equation in Table 1). A reaction period as short as 0.5 h is satisfactory (cf. entries 5 and 6), but longer times, up to 7 h, were generally used to ensure the completion of the reaction. Bromopropynamide **9** is a better acetylenic substrate than the corresponding ethyl ester **14** (entry 7). With this combination of substrates and reaction conditions, the desired product **13** was obtained in 70% yield. Under similar reaction conditions, other propynamides **16**–**18** afforded the desired products **19**–**21** in good yields (entries 8–10).[7]

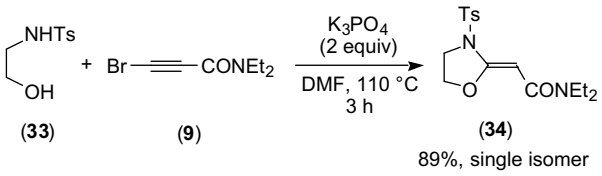
Although the tosyl protection of the diamine, such as in **12**, proved to be essential for the success of the reaction, we found that both tosyl groups in **12** are not necessary. Thus, a mono-tosylated diamine having another protective group still effected the desired reaction. For instance, Ts- and Boc-protected diamine **22** afforded the desired product **23** in a satisfactory yield and, surprisingly, as a single stereoisomer (Table 1, entry 11). The stereochemistry of its olefin moiety was assigned as *E* by a NOESY experiment that showed the correlation between the vinyl proton and *ortho*-protons of the Ts group. Similarly, unsymmetrical imidazolidines **24**–**26** were prepared from the corresponding bromoacetylenic amides **16**–**18** (entries 12–14).[7,8]

This reaction should proceed according to Scheme 3. The sulfonamide moiety of **27**, under any condition, takes part in the first conjugate addition/elimination sequence to produce β-(sulfonylamino)propynamide **28**. The second intramolecular addition of another amido group in **28** forms enolate **29**–**31**, protonation of which most likely determines the stereochemistry of the product to produce sterically less hindered **32** (X = Boc).

The reaction course shown in Scheme 3 suggests that the second nucleophilic addition (i.e., from **28** to **29**) might be feasible with other heteroatom functional groups. This expectation was realized when N-tosylated aminoalcohol **33** entered the reaction to produce oxazolidine derivative **34** in excellent yield as a single isomer (Scheme 4).[9] Its



Scheme 3.



Scheme 4.

olefinic stereochemistry was assigned as *Z* by a NOESY experiment.[10]

In summary, 2-alkylidene-1,3-imidazolidines were conveniently prepared from suitably protected 1,2-diamines and bromoproynamides. Further investigation of synthetic applications of this reaction and its products is now under way.

Acknowledgments

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References and notes

1. For reviews on imidazolidines of structure **3**, see: (a) Wang, M.; Huang, Z. *Prog. Nat. Sci.* **2002**, *12*, 249–257; (b) Huang, Z.-T.; Wang, M.-X. *Heterocycles* **1994**, *37*, 1233–1262. For reviews on imidazolidines, see: (c) Huang, Z.-T.; Wang, M.-X. In *The Chemistry of Enamies*; Rappoport, Z., Ed.; Wiley Interscience: London, 1994; pp 1303–1363; (d) Katritzky, A. R., Rees, C. W., Eds. Comprehensive Heterocyclic Chemistry; Pergamon Press: Oxford, 1984; Vol. 5.
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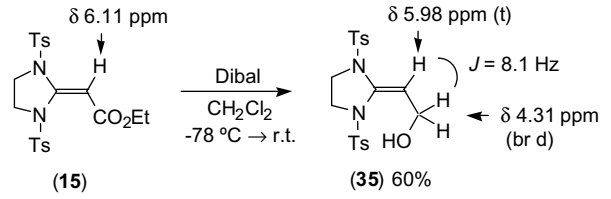
3. The parent **3** and its protected derivatives are a versatile building block for the construction of five-membered diazacycles. For representative synthetic applications, see: (a) Yu, C.-Y.; Yang, P.-H.; Zhao, M.-X.; Huang, Z.-T. *Synlett* **2006**, 1835–1840; (b) Jones, R. C. F.; Patel, P.; Hirst, S. C.; Smallridge, M. J. *Tetrahedron* **1998**, *54*, 6191–6200; (c) Jones, R. C. F.; Turner, I.; Howard, K. J. *Tetrahedron Lett.* **1993**, *34*, 6329–6332; (d) Jones, R. C. F.; Hirst, S. C. *Tetrahedron Lett.* **1989**, *30*, 5361–5364; (e) Jones, R. C. F.; Hirst, S. C. *Tetrahedron Lett.* **1989**, *30*, 5365–5368; (f) Jones, R. C. F.; Smallridge, M. J. *Tetrahedron Lett.* **1988**, *29*, 5005–5008.
4. For mono-protected form of **3**, see: Ref. 3. For other preparations of derivatives of **3**, see: (a) Shubina, Y. V.; Tikhomirov, D. A.; Eremeev, A. V. *Khim. Geterotsikl. Soedin.* **1985**, 618–622; *Chem. Heterocycl. Comp.* **1985**, *21*, 516–520; (b) Wang, H.-T.; Wang, X.-J.; Huang, Z.-T. *Chem. Ber.* **1990**, *123*, 2141–2145; (c) Dannhardt, G.; Laufer, S.; Ziereis, K. *Arch. Pharm.* **1988**, *321*, 429–430; (d) Huang, Z.-T.; Tzai, L.-H. *Chem. Ber.* **1986**, *119*, 2208–2219; (e) Anderson, M. W.; Begley, M. J.; Jones, R. C. F.; Saunders, J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2599–2602. For mono-protection of relevant ketones, see: (g) Wang, M.-X.; Wu, X.-D.; Wang, L.-B.; Huang, Z.-T. *Synth. Commun.* **1995**, *25*, 343–349; (h) Wang, M.-X.; Huang, Z.-T. *J. Org. Chem.* **1995**, *60*, 2807–2811; (i) Ren, Z.-X.; Li, Z.-J.; Huang, Z.-T. *Synth. Commun.* **1998**, *28*, 4241–4247.
5. For structural confirmation, product **15** was reduced with Dibal to give allylic alcohol **35**, which was consistent with the expected structure by ^{1}H NMR analysis.



(**15**) (**35**) 60%

6. In addition, *N,N′*-bis(*o*-nitrobenzenesulfonyl)ethylenediamine (di-Ns-substituted **1**) did not give the desired product in more than a trace amount. Thus, acyl and sulfonyl derivatives of **1** having a less or more acidic amide proton than that of **12** appear not to participate in this conjugate addition.
7. *Typical procedures for the preparation of* **13** *and* **23** *are as follows: N,N-Diethyl-2-[1,3-di(p-toluenesulfonyl)imidazolidin-2-ylidene]acetamide* (**13**): To a solution of *N,N′*-di(*p*-toluenesulfonyl)ethylenediamine (**12**) (73.7 mg, 0.200 mmol) and K_3PO_4 (84.9 mg, 0.400 mmol) in DMF (2.0 mL) in an oil bath maintained at 100 °C was added *N,N*-diethylbromopropynamide (**9**) (44.8 mg, 0.220 mmol) in DMF (2.0 mL) under argon. The reaction mixture was stirred at the same temperature for 7 h. After being cooled to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give a crude oil, which was chromatographed on silica gel (hexane–ethyl acetate) to afford the title compound (68.5 mg, 70%) as a solid. ^{1}H NMR δ 1.12 (t, $J = 7.2$ Hz, 3H), 1.23 (t, $J = 7.2$ Hz, 3H), 2.40 (s, 3H), 2.41 (s, 3H), 3.27–3.45 (m, 8H), 6.28 (s, 1H), 7.27 (d, $J = 8.4$ Hz, 2H), 7.32 (d, $J = 8.4$ Hz, 2H), 7.73 (d, $J = 8.4$ Hz, 2H), 7.82 (d, $J = 8.4$ Hz, 2H). ^{13}C NMR δ 12.57, 13.87, 21.58 (2 peaks), 39.28, 42.26, 45.86, 46.50, 97.72, 127.39, 128.03, 129.79, 130.00, 134.36, 134.98, 138.69, 144.74, 145.07, 165.37. IR (Nujol) 2925, 2854, 1663 (C=O), 1623, 1598, 1365, 1338, 1320, 1261, 1164, 1138, 1087, 1046, 829 cm^{-1}. Anal. Calcd for $C_{23}H_{29}N_3O_5S_2$: C, 56.19; H, 5.95. Found: C, 55.89; H, 6.14. Mp 103–105 °C. *(E)-N,N-Diethyl-[3-(tert-butyloxycarbonyl)-1-(p-toluenesulfonyl)imidazolidin-2-ylidene]acetamide*(**23**): To a solution of *N*-(*t*-butyloxycarbonyl)-*N′*-(*p*-toluenesulfonyl)ethylenediamine (**22**) (62.9 mg, 0.200 mmol) and K_3PO_4 (84.9 mg, 0.400 mmol) in DMF (2.0 mL) in an oil bath maintained at 70 °C was added *N,N*-diethylbromopropynamide (**9**) (44.9 mg, 0.220 mmol) in DMF (2.0 mL) under argon. The reaction mixture was stirred at the same temperature for 0.5 h. After being cooled to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give a crude oil, which was chromatographed on silica gel (hexane–ethyl acetate) to afford the title compound (59.2 mg, 68%) as a solid. ^{1}H NMR δ 1.14 (t, $J = 7.2$ Hz, 3H), 1.23 (t, $J = 7.2$ Hz, 3H), 1.36 (s, 9H), 2.41 (s, 3H), 3.32–3.72 (m, 8H), 6.04 (s, 1H), 7.30 (d, $J = 8.4$ Hz, 2H), 7.74 (d, $J = 8.4$ Hz, 2H). NOESY experiments showed the correlation between the peaks at δ 6.04 ppm (vinyl H) and at δ 7.74 ppm (*ortho*-protons of the Ts group). Thus, the stereochemistry of the olefin moiety was assigned to be *E*. ^{13}C NMR δ 13.05, 14.07, 21.51, 27.96, 39.53, 42.47, 44.56, 45.38, 81.80, 92.36, 127.39, 129.92, 134.38, 139.99, 144.76, 150.40, 165.60. IR (Nujol) 3167, 2978, 2933, 2240, 1734 (C=O), 1653 (C=O), 1617, 1457, 1363, 1261, 1164, 1090, 953, 918, 848, 816 cm^{-1}. Anal. Calcd for $C_{21}H_{31}N_3O_5S$: C, 57.64; H, 7.14. Found: C, 57.48; H, 6.76. Mp 44–48 °C.
8. For the deprotection of Ts and Boc groups, see: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991; pp 379–385, 387.
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10. A correlation between the vinyl proton and *ortho*-protons of the tosyl group was observed.