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A novel synthesis of 2-alkyl(aryl)pyrrolidines from proline *via* 2,3-diphenylhexahydropyrrolo[2,1-*b*]oxazoles

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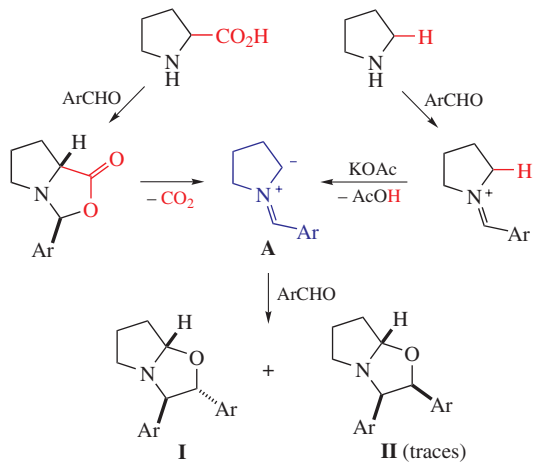
Diphenyloxapyrrolizidines, products of the reaction between proline and benzaldehyde, are convenient building blocks for synthesizing 2-substituted pyrrolidines. The opening of their oxazolidine ring by treatment with Grignard reagents has been performed and conditions for subsequent removal of the *N*-hydroxyethyl moiety have been found. Though the yields are moderate (36–42%), the suggested synthesis of 2-alkyl(aryl)pyrrolidines is rather simple since it does not require purification of intermediate products and is easy scalable.

α-Substituted pyrrolidine moiety is incorporated in many natural alkaloids and compounds with high biological activity.[1–3] The principal syntheses of such compounds are documented.[1–7] Enantioselective synthesis of 2-substituted pyrrolidines from (*R*)-(–)-2-phenylglycinol and 3-acylpropionic acids involving two subsequent reduction stages was suggested by Burgess and Meyers.[8] The approach implemented by Seidel *et al*.[9] is most similar to the synthesis of 2-R-pyrrolidines that we suggested. They carried out a decarboxylative Strecker reaction of proline with benzaldehyde in the presence of cyanide anion to give the corresponding α-amino nitrile, which was then used in the Bruylants reaction with Grignard reagents.[9(b)] Though the methods to synthesize the pyrrolidine system are rather abundant, its simplest α-substituted derivatives are still hardly available and expensive. This fact gives an impetus to a search for new methods of their synthesis.

On the other hand, 5-aryloxazolidines, saturated heterocycles little studied before our publications,[10] are readily formed in reactions of nonstabilized azomethine ylides with carbonyl compounds.[11] We turned our attention to a study by Orsini (Scheme 1) where proline reacted with aromatic aldehydes in DMSO to afford oxapyrrolizidines **I** and **II** with high regio- and stereoselectivity.[11(c)] Hajra *et al*. elaborated a synthesis of oxapyrrolizidines **I** by treatment of pyrrolidine with aromatic aldehydes in toluene under microwave irradiation.[12] In both cases, nonstabilized azomethine ylide **A** is formed, which then undergoes [3+2]-cycloaddition with a second molecule of the aldehyde.



Scheme 1

However, though these compounds are easy to obtain and the node carbon atom has a semi-aminal nature, the feasibility of using these compounds as the key building blocks to synthesize 2-alkyl(aryl)pyrrolidines was not examined.

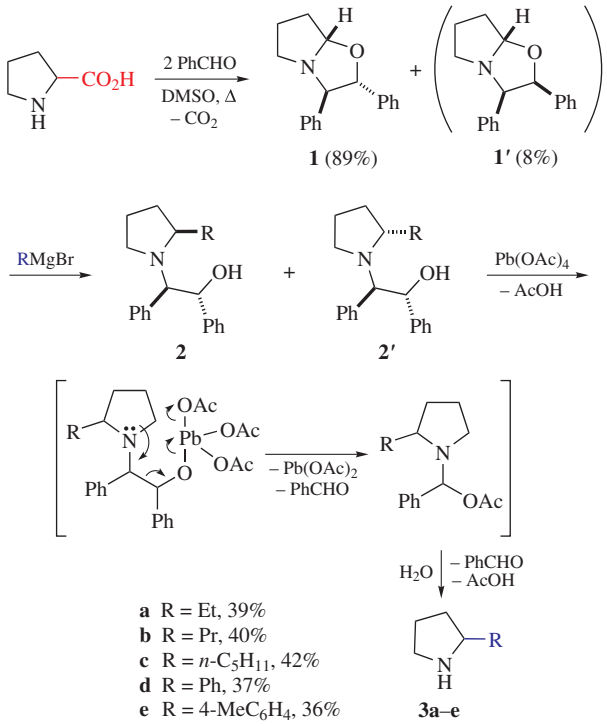
In our studies, we used a readily available adduct **I** (Ar = Ph) and repeated Orsini's reaction with larger amounts of proline (0.287 mol) and benzaldehyde (0.573 mol). The crude product (^{1}H NMR) was a mixture of stereoisomeric oxapyrrolizidines **1** (89%), **1′** (8%) and traces of the starting benzaldehyde (3%). Since conversion with respect to benzaldehyde was high (98%) and the crude product was a thick yellow oil, we used it in the next stage without purification.

Taking into account the enhanced electrophilicity of the amino acetal nodal carbon atom in isomers **1** and **1′**, it could be expected that their reactions with Grignard reagents would involve oxapyrrolizidine ring opening to yield 1,2-disubstituted pyrrolidines. In fact, the reaction with ethylmagnesium bromide (2.0 equiv.) gave a viscous liquid that was a mixture of two isomeric amino alcohols **2** and **2′** (R = Et) with a conversion of 95% (Scheme 2).

In the final third stage of the synthesis of 2-ethylpyrrolidine **3a**, we had to remove the hydroxy(diphenyl)ethyl substituent from the nitrogen atom. The best result was achieved on driving the vicinal C–C cleavage with lead tetraacetate (1.35 equiv.) in

† *General procedure*. Proline (33.0 g, 0.287 mol), benzaldehyde (58.5 ml, 60.8 g, 0.573 mol) and DMSO (330 ml) were placed in a round-bottom one-necked 1 dm^3 flask equipped with a reflux condenser. The mixture was heated with magnetic stirring in a glycerol bath at 90–97 °C for 1 h. The resulting solution was cooled, diluted with water (500 ml) and extracted with Et_2O (3×130 ml). The extract was dried with Na_2SO_4. The solvent was removed *in vacuo*. The resulting mixture of isomeric oxapyrrolizidines **1** and **1′** (75 g) obtained as a light-yellow thick oil was dissolved in 220 ml of dry PhMe to make dosing more convenient. It was used in the next stage without any purification.

Part of the previously prepared solution of oxapyrrolizidines **1** and **1′** (50 mmol) in toluene was placed in a 250 ml round-bottom flask equipped with a dropping funnel, reflux condenser and magnetic stirrer. The mixture was cooled with an ice salt bath. A solution of pre-prepared RMgBr (100 mmol, 2 equiv.) from equal molar amounts of an appropriate RBr and magnesium turnings in dry Et_2O (for bromoalkanes) or dry THF (for bromoarenes) was slowly added to the solution. The ice bath was removed and the mixture was refluxed for 15 min, then cooled with ice once more. Excess saturated NH_4Cl solution was added from the dropping funnel. The organic layer was separated and the aqueous layer was extracted with a small amount of PhMe. The extracts were dried with Na_2SO_4, then the solvents were removed *in vacuo* to give a mixture of isomeric amino alcohols **2** and **2′** as a thick light-yellow oil.



Scheme 2

toluene on cooling. Using this method, 2-ethylpyrrolidine **3a** was obtained in 39% yield after fractional distillation.† A likely mechanism of the redox process is shown in Scheme 2. In fact, it is a modification of the known Criegee cleavage of 1,2-diols, where the nitrogen atom acts as an electron donor in the initial process stage. Of the reported methods for amino alcohol cleavage,[13] we also used acid dehydration followed by hydrolysis, oxidative cleavage with potassium dichromate with subsequent heating in sulfuric acid, and treatment with cerium ammonium nitrate in a water–acetonitrile mixture. Neither of these methods provided usable results (see Table S1, Online Supplementary Materials).

Similarly, 2-propylpyrrolidine **3b** was obtained in 40% yield. Interestingly, 2-alkylpyrrolidines **3a**,**b** give low-boiling (up to 115 °C) mixtures with water. We failed to isolate them in pure form, neither by prolonged drying of an ethereal extract of the crude product with KOH/NaOH, nor by replacement of the solvent by hexane. Eventually we had to introduce a stage of picrate preparation. Furthermore, pyrrolidines **3a**,**b** give hygroscopic hydrooxalates, which can be dried only by prolonged heating at 60–110 °C in a rotary evaporator.

2-Pentylpyrrolidine **3c** that has a higher boiling point was fractionated *in vacuo* of a water-jet pump and was isolated in 42% yield. Using a similar approach, we obtained 2-phenyl- and 2-(*p*-tolyl)pyrrolidines **3d** and **3e** in 37 and 36% yields, respectively (purification was carried out by distillation under reduced pressure).‡ Note that all the yields indicated were calculated with respect to the starting proline. Since the described method does not require purification of intermediate products, it is rather simple to perform and can easily be scaled for even larger loads.

In conclusion, we proposed a new three-stage protocol for the preparation of 2-substituted pyrrolidines from proline, benzaldehyde and Grignard reagents. It formally looks like replacement of the carboxy group in proline by a hydrocarbon residue and makes available a series of simplest 2-alkyl- and 2-arylpyrrolidines that can be of interest for synthesizing more complex molecules with potential biological activity.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2015.11.014.

References

1 (*a*) A. O. Plunkett, *Nat. Prod. Rep*., 1994, **11**, 581; (*b*) G. Pandey, P. Banerjee and S. R. Gadre, *Chem. Rev.*, 2006, **106**, 4484; (*c*) A. Mitchinson and A. Nadin, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2862.
2 *Tobacco Alkaloids and Related Compounds*, ed. U. S. von Euler, Pergamon, New York, 1965.
3 N. E. Shevchenko, K. Vlasov, V. G. Nenajdenko and G.-V. Röschenthaler, *Tetrahedron*, 2011, **67**, 69.
4 L. C. Craig, H. Bulbrook and R. M. Hixon, *J. Am. Chem. Soc*., 1931, **53**, 1831.
5 J. H. Burckhalter and J. H. Short, *J. Org. Chem*., 1958, **23**, 1281.
6 K. L. Sorgi, C. A. Maryanoff, D. F. McComsey and B. E. Maryanoff, *Org. Synth*., 1998, **75**, 215.
7 (*a*) C. J. Dunsmore, R. Carr, T. Fleming and N. J. Turner, *J. Am. Chem. Soc.*, 2006, **128**, 2224; (*b*) J. I. Seeman, *Synthesis*, 1977, 498; (*c*) D. H. Hua, S. W. Miao, S. N. Bharathi, T. Katsuhira and A. A. Bravo, *J. Org. Chem*., 1990, **55**, 3682; (*d*) C. A. Willoughby and S. L. Buchwald, *J. Org. Chem*., 1993, **58**, 7627.
8 L. E. Burgess and A. I. Meyers, *J. Org. Chem*., 1992, **57**, 1656.
9 (*a*) C. Zhang and D. Seidel, *J. Am. Chem. Soc*., 2010, **132**, 1798; (*b*) D. Das, M. T. Richers, L. Ma and D. Seidel, *Org. Lett.*, 2011, **13**, 6584; (*c*) L. Ma, W. Chen and D. Seidel, *J. Am. Chem. Soc.*, 2012, **134**, 15305; (*d*) D. Das, A. X. Sun and D. Seidel, *Angew. Chem. Int. Ed*., 2013, **52**, 3765; (*e*) W. Chen, R. G. Wilde and D. Seidel, *Org. Lett.*, 2014, **16**, 730; (*f*) D. Seidel, *Acc. Chem. Res.*, 2015, **48**, 317.
10 (*a*) V. S. Moshkin and V. Y. Sosnovskikh, *Tetrahedron Lett*., 2013, **54**, 2455; (*b*) V. S. Moshkin and V. Y. Sosnovskikh, *Tetrahedron Lett*., 2013, **54**, 2699; (*c*) V. S. Moshkin and V. Y. Sosnovskikh, *Tetrahedron Lett.*, 2014, **55**, 6121; (*d*) V. Y. Sosnovskikh, M. Y. Kornev and V. S. Moshkin, *Tetrahedron Lett*., 2014, **55**, 212; (*e*) V. Y. Sosnovskikh, M. Y. Kornev, V. S. Moshkin and E. M. Buev, *Tetrahedron*, 2014, **70**, 9253.

The mixture of amino alcohols **2** and **2′** (50 mmol) was dissolved in 60 ml of PhMe in a round-bottom one-necked 250 ml flask, cooled in an ice-salt bath, and $Pb(OAc)_4$ (29.9 g, 67.5 mmol, 1.35 equiv.) was added in portions with stirring. The mixture was allowed to warm to room temperature and stirred for 1 h. Concentrated HCl (29 ml) and water (100 ml) were added, and the mixture was boiled for 15 min. After cooling to room temperature, the aqueous and toluene layers were decanted from the remaining $PbCl_2$ + resin. The remaining product was extracted with an additional amount of water (30 ml) from the residue in the flask; the extraction was carried out with heating and stirring followed by cooling. All the liquid phases were combined, toluene was separated, and the aqueous layer was extracted with diethyl ether (2×25 ml). A large excess of NaOH (60 g, 1.5 mol) was added to the solution. Pyrrolidine **3** that separated was extracted with diethyl ether (2×25 ml). The extract was dried and fractionally distilled.

‡ *2-Pentylpyrrolidine* **3c**. Yield 42%, colourless liquid, bp 70–75 °C/10 Torr (lit.,[14] bp 153 °C/760 Torr). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.89 (t, 3H, Me, *J* 6.9 Hz), 1.22 (ddt, 1H, *J* 12.2, 9.3 and 8.0 Hz), 1.26–1.50 (m, 8H), 1.65–1.79 (m, 2H), 1.82–1.91 (m, 2H), 2.81 (ddd, 1H, C*H*HN, *J* 10.5, 8.0 and 7.1 Hz), 2.92 (quintet, 1H, CHN, *J* 6.9 Hz), 3.01 (ddd, 1H, CH*H*N, *J* 10.5, 7.6 and 5.3 Hz).

2-Phenylpyrrolidine **3d**. Yield 37%, colourless liquid, bp 102–106 °C/10 Torr (lit.,[15] bp 104–108 °C/10 Torr), picrate mp 147–150 °C (lit.,[5] bp 148–149 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.61–1.73 (m, 1H), 1.79–1.98 (m, 2H), 2.13–2.23 (m, 1H), 2.25 (s, 1H, NH), 3.01 (ddd, 1H, C*H*HN, *J* 10.1, 8.2 and 6.8 Hz), 3.20 (ddd, 1H, CH*H*N, *J* 10.1, 7.7 and 5.3 Hz), 4.11 (t, 1H, CHN, *J* 7.7 Hz), 7.22 (tt, 1H, Ph, *J* 7.1 and 1.6 Hz), 7.28–7.38 (m, 4H, Ph).

2-(p-Tolyl)pyrrolidine **3e**. Yield 36%, colourless liquid, bp 120–123 °C/10 Torr (lit.,[16] bp 128–130 °C/9 Torr). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.60–1.67 (m, 1H), 1.78–1.95 (m, 2H), 1.99 (s, 1H, NH), 2.11–2.19 (m, 1H), 2.32 (s, 3H, Me), 2.98 (ddd, 1H, C*H*HN, *J* 10.1, 8.3 and 6.9 Hz), 3.19 (ddd, 1H, CH*H*N, *J* 10.1, 7.8 and 5.2 Hz), 4.06 (t, 1H, CHN, *J* 7.7 Hz), 7.12 (d, 2H, Ar, *J* 8.0 Hz), 7.24 (d, 2H, Ar, *J* 8.0 Hz).

11 (*a*) G. P. Rizzi, *J. Org. Chem*., 1970, **35**, 2069; (*b*) A. Padwa and W. Dent, *J. Org. Chem.*, 1987, **52**, 235; (*c*) F. Orsini, F. Pelizzoni, M. Forte, R. Destro and P. Gariboldi, *Tetrahedron*, 1988, **44**, 519; (*d*) M. Nyerges, I. Fejes, A. Virányi, P. W. Groundwater and L. Töke, *Synthesis*, 2001, 1479; (*e*) J. H. Ryan, N. Spiccia, L. S.-M. Wong and A. B. Holmes, *Aust. J. Chem*., 2007, **60**, 898.

12 M. Rahman, A. K. Bagdi, S. Mishra and A. Hajra, *Chem. Commun.*, 2014, **50**, 2951.

13 (*a*) L. Guerrier, J. Royer, D. S. Grierson and H.-P. Husson, *J. Am. Chem. Soc*., 1983, **105**, 7754; (*b*) A. Cisneros, S. Fernández and J. E. Hernández, *Synth. Commun*., 1982, **12**, 833; (*c*) Y. Génisson, M. Mehmandoust, C. Marazano and B. C. Das, *Heterocycles*, 1994, **39**, 811; (*d*) C. Agami, F. Couty and G. Evano, *Tetrahedron Lett*., 1999, **40**, 3709; (*e*) H. Fujioka, H. Hirose, Y. Ohba, K. Murai, K. Nakahara and Y. Kita, *Tetrahedron*, 2007, **63**, 625; (*f*) H. Poerwono, K. Higashiyama, T. Yamauchi, H. Kubo, S. Ohmiya and H. Takahashi, *Tetrahedron*, 1998, **54**, 13955; (*g*) T. Kobayashi, F. Hasegawa, Y. Hirose, K. Tanaka, H. Mori and S. Katsumura, *J. Org. Chem*., 2012, **77**, 1812; (*h*) H. Takahashi, B. C. Hsieh and K. Higashiyama, *Chem. Pharm. Bull*., 1990, **38**, 2429.

14 J. M. Patterson, J. Brasch and P. Drenchko, *J. Org. Chem.*, 1962, **27**, 1652.

15 M. Malmberg and K. Nyberg, *Acta Chem. Scand., Ser. B*, 1981, **35**, 411.

16 D. F. Starr, H. Bulbrook and R. M. Hixon, *J. Am. Chem. Soc.*, 1932, **54**, 3971.

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