Tetrahedron Letters, Vol. 33, No. 52, pp. 8125-8126, 1992
Printed in Great Britain

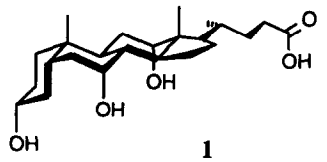
0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Protection of Primary Amino as Pyrrole in Organometallic Reagents

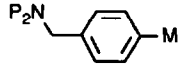
Anthony P. Davis* and Thomas J. Egan
Department of Chemistry, Trinity College, Dublin 2, Ireland

Abstract: *Pyrrole* **5** *was converted into Grignard and organocuprate reagents. After addition of the latter to alkene* **6**, *the pyrrole ring was converted to a primary amine by ozonolysis, reduction and hydrolysis.*

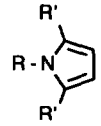
In the course of our programme on the synthesis of "cholaphanes", macrocyclic host molecules derived from cholic acid (**1**),[1] we have required synthons of the general form **2** for use in the introduction of a spacer unit at the steroidal C3. This need has alerted us to the general shortage of *N*-protecting groups which are stable to strongly basic (e.g. organolithium or Grignard) reagents.[2] The problem is particularly acute if it is necessary to eliminate the basicity/coordinating properties of the N-lone pair on protection. For example, while we have been able to use silicon-based protecting groups in **2** (M = Li, Mn),[1a] analogous organocopper reagents have been found to be unreactive (presumably because of N→Cu coordination).



1



2 M = metal
P = protecting group



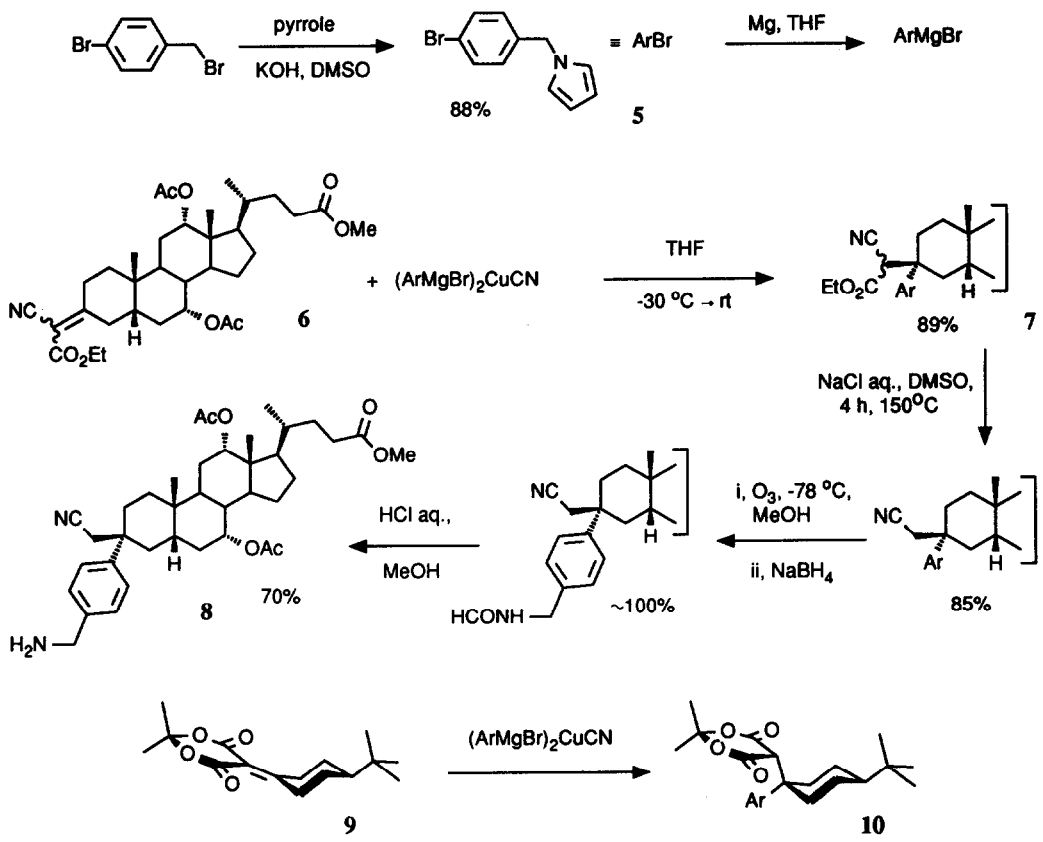
3 R' = CH_3
4 R' = H

Possibly the only protection method which suppresses both the acidity and basicity of an amino group, and is also compatible with strongly basic reagents, is incorporation in a pyrrole ring. In the original version,[3] this protocol involved treatment of the amine RNH_2 with hexane-2,5-dione to give 2,5-dimethylpyrrole **3**, and reversal by treatment with $HONH_2.HCl/KOH$ in $EtOH/H_2O$ (prolonged reflux). The latter procedure is somewhat agressive, so that the method is rather limited in its applicability. However, our attention was caught by a more recent paper in which the pyrrole ring was proposed as a protecting group in peptide synthesis.[4] This work contained two significant developments. Firstly, in addition to protecting the amines as **3**, they were also converted to less substituted analogues **4**. Secondly, the deprotection method involved ozonolysis/reduction to an amide, and hydrolysis of the latter. In the case of **4** the corresponding amide was a formamide, which could be cleaved under relatively mild conditions.[5]

It seemed that, provided **4** could be used in conjunction with an organometallic centre, it would occupy a unique position in synthetic organic methodology. We now report experiments which demonstrate that protection as pyrrole can be used in synthons **2**, that it is compatible with an organocuprate, and that removal can be accomplished in the presence of a number of functional groups.

Our more important results are summarised in the Scheme. Bromide **5** was prepared by an adaptation

of a literature procedure[6] and was converted smoothly to the corresponding Grignard reagent at room temperature in THF (~1 h, monitored by GC). After quenching with D_2O, NMR spectra showed no sign of D-incorporation in the pyrrole ring. The derived higher-order cuprate added to Knoevenagel products **6** and **9** to give **7** and **10** respectively,[7] and could also be silylated with Me_3SiCl. Deprotection was accomplished in the case of **7**, after removal of an unwanted asymmetric centre by deethoxycarbonylation, leading to cholaphane precursor **8** in a very acceptable overall yield.[8]



References and Footnotes.

1. (a) Bonar-Law, R.P.; Davis, A.P., *J. Chem. Soc., Chem. Commun.* **1989**, 1050. (b) Davis, A.P.; Orchard, M.G.; Slawin, A.M.Z.; Williams, D.J. *J. Chem. Soc., Chem. Commun.* **1991**, 612.
2. For a more complete discussion of the problem, see: Bonar-Law, R.P.; Davis, A.P.; Dorgan, B.J. *Tetrahedron Lett.* **1990**, *31*, 6721.
3. Bruekelman, S.P.; Leach, S.E.;Meakins, G.D.; Tirel, M.D. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2801.
4. Kashima, C.; Maruyama, T.; Harada, K.; Hibi, S.; Omote, Y. *J. Chem. Res. (S)* **1988**, 62; *(M)* 0601.
5. For alternative deformylation methods, see: Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis* (2nd edn.); Wiley-Interscience: New York, 1991; p. 350.
6. Heaney, H.; Ley, S.V. *J. Chem. Soc., Perkin Trans 1* **1973**, 499.
7. *cf.* ref 1b. This type of reaction will be discussed in greater detail in a separate publication.

8. We thank EOLAS, the Irish Science and Technology Agency, for financial support of this work.

(Received in UK 1 October 1992)