Pergamon

Tetrahedron Letters 41 (2000) 1833–1836

TETRAHEDRON LETTERS

Replacing tin in radical chemistry: *N*-ethylpiperidine hypophosphite in cyclisation reactions of aryl radicals

Concepcion Gonzalez Martin, John A. Murphy * and Christopher R. Smith

Department of Pure and Applied Chemistry, University of Strathclyde, 295 Cathedral St., Glasgow G1 1XL, UK

Received 19 November 1999; accepted 21 December 1999

Abstract

A detailed study of aryl radical cyclisations using *N*-ethylpiperidine hypophosphite shows that the reagent has advantages over tributyltin hydride in radical generation and reaction.

The advances made over the past 30 years in carbon–carbon bond formation mediated by free radical chemistry using organotin reagents have been impressive. However, problems in separation of reaction products from organotin contaminants and the toxicity of the tin reagents and by-products[1,2] have prevented their application to pharmaceutical manufacture. Recently many highly original alternative reagents[3,4] and processes for free radical chemistry have been described. Our own interests have focused on tetrathiafulvalene,[5] which allows for oxidative termination of the radical process, and, more recently, on hypophosphorous acid and its *N*-ethylpiperidine salt[6] (EPHP) which provide reductive termination. Barton et al.[7] and Jang[8] had used these phosphorus reagents for radical defunctionalisation reactions, but not for C–C bond formation. Barton et al.[7] describe rapid addition of phosphorus-centred radicals to alkenes, and this may have deterred them from investigating C–C bond formation using these reagents. However a number of recent studies demonstrate that this does not present a problem in cyclisation of simple substrates.[6,9] The low cost of the phosphorus reagents and their ease of separation from reaction products heralds a new era where radical reactions forming C–C bonds are both economical and convenient.

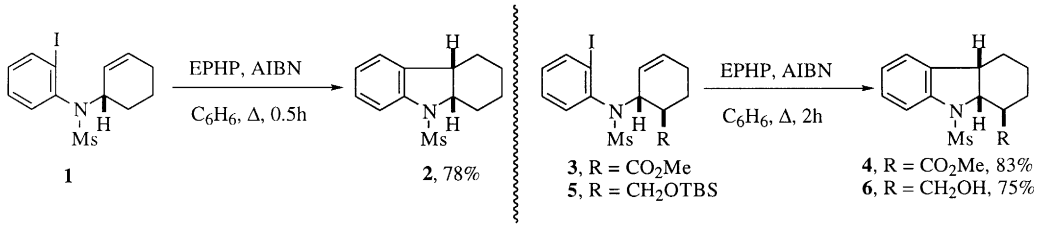
Reactions are usually performed with 10 equiv. of EPHP. The current paper uses fairly complex substrates which are useful in synthesis of complex alkaloids: (i) to examine the effect of decreasing the number of equivalents of EPHP; (ii) to present easily attacked terminal alkenes to the intermediate phosphorus radicals to see if phosphorus radical addition to the alkenes prevails over the desired cyclisation reactions; and (iii) to make direct comparisons with tributyltin hydride.

The first set of substrates, **1**, **3** and **5**, afforded cyclisations onto an H-substituted cyclohexene carbon. The cyclisations proceed very efficiently to form the expected *cis*-fused hexahydrocarbazoles.

* Corresponding author.

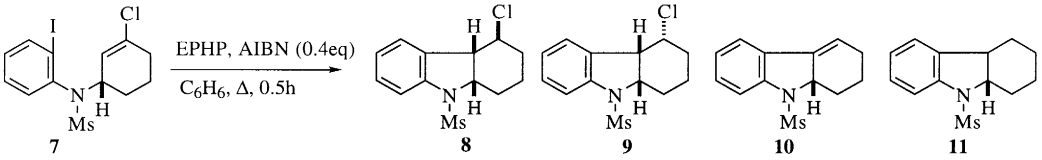
0040-4039/00/$ - see front matter
PII: S0040-4039(00)00010-1

Deprotection was observed when the TBS ether **3** was subjected to the reaction. Blank experiments have shown that this deprotection arises from the acidity of the EPHP, which is the monosalt of a dibasic acid.



1 **2**, 78% **3**, R = CO_2Me **5**, R = CH_2OTBS **4**, R = CO_2Me, 83% **6**, R = CH_2OH, 75%

Since each molecule of EPHP has two hydrogens which can be used in reduction, and since 10 equiv. were used, this means that the reactions were conducted with a 20-fold excess of H-atom source — hence the effect of using less reagent was explored with **7**. As shown below, decreasing from 10 equiv. to 5 equiv. led to a slight improvement in yield but a significant increase in reaction time, *t*, to complete conversion. A further decrease to 3 equiv. slowed the reaction further still, and considerable amounts of the product of elimination **10** were observed after 24 h. Using just 1 equiv. afforded 31% of product together with 64% of **7** after 48 h, so the reaction was halted well before complete conversion. The cyclisation of this substrate was also studied with tributyltin hydride, and intriguingly this showed a lowered chemoselectivity, with substantial reduction of the aliphatic C–Cl bond being observed by the time that conversion of **7** was complete. Barton et al.[7] had previously described the difference in reactivity of phosphorus radicals towards carbon–halogen bonds, and the complete stability of the C–Cl bond under these conditions offers clear synthetic opportunities which we are currently investigating.



7 **8** **9** **10** **11**

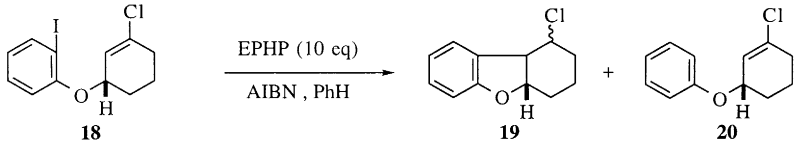
EPHP (10 equiv), reaction time t = 1h	67%	9%	0%	0%
EPHP (5 equiv), t = 5h	69%	9%	0%	0%
EPHP (3 equiv), t = 24h	65%	10%	10%	0%
EPHP (1 equiv), t = 48h (64% recovery of **7**)	31%	3%	0%	0%
TBTH (1.1 equiv) 0.01M, AIBN (0.2equiv) t = 1h added in one go	35%	3%	0%	40%
TBTH (1.1 equiv) 0.01M, AIBN (0.2equiv) syringe pump addition over 2h, t = 3h	32%	2%	0%	37%

The effect of increased steric crowding in the substrate was next studied using substrates **12**–**14**. The more congested cyclohexene π-bond should slow the cyclisation reactions and give more opportunity for reduction prior to cyclisation. These substrates also featured terminal alkenes, and so would provide an alternative way for the yields of the desired cyclisation products to be decreased, through addition of the intermediate phosphorus radicals to the alkene. In practice, the cyclisations proceeded well with EPHP giving 71% and 68% of **15** and **16**, respectively. Substrate **14** was used to compare EPHP with the organotin reagent, with a slightly higher yield being observed for the EPHP reaction. In contrast to the case of **7** above, the (neopentyl) chlorine atom in **17** was not reduced by tributyltin hydride in this case, presumably because of the greater steric crowding around that atom.

12 X = R = H
13 X = H, R = CH_2OTBS
14 X = Cl, R = H

15 X = R = H (EPHP, 71%)
16 X = H, R = CH_2OH (EPHP, 68%)
17 X = Cl, R = H (EPHP, 61%; TBTH, 56%)

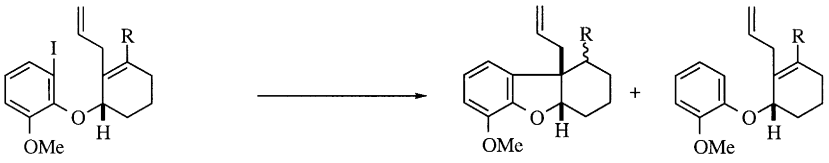
The chemistry was then extended to the related oxygen series, which showed rather different results. Initial cyclisation of **18** gave poorer yields of cyclised product **19** compared to the nitrogen series. [This suggested a slower cyclisation[10] for *O*- versus *N*- substrates]. However, a slower addition of EPHP and AIBN by syringe-pump dramatically improved the yield to 80%.



18 **19** **20**

reaction time, t = 1h	42%	18%
syringe-pump addn over 2h, t = 2.5h	80%	7%

When the cyclohexene double bond of the substrate bore an allyl group, the relative amount of reduced uncyclised product increased as expected. Substrate **21** afforded 43% of cyclised product **24**, and 24% of reduced product **25**. [This was slightly better than was found with tributyltin hydride.] Substituting the cyclohexene double bond with either a chlorine atom or a sulfone group as in **22** and **23** did not lead to increased yields of cyclised products.



21, R = H, EPHP, (10 eq.), t = 6h, AIBN (0.4 eq.)	**24**, 43%	**25**, 24%
21, R = H, TBTH (1.1 eq.), t = 2.5h, AIBN (0.2 eq.)	**26**, 34%	**27**, 21%
22, R = Cl, EPHP, (10 eq.), t = 6h, AIBN (0.4 eq.)	**28**, 29%	**29**, 17%
23, R = SO_2Ph, EPHP, (10 eq.), t = 6h, AIBN (0.4 eq.)	**30**, 41%	**31**, 20%

In summary, this study shows that respectable yields of cyclised materials are isolated, even when the substrates present terminal alkenes to the phosphorus reagent. So, adducts resulting from attack of the EPHP radicals on the alkenes have not presented serious competition. Furthermore, whereas tributyltin radicals reduce aryl iodide and alkyl chloride at apparently competitive rates, the phosphorus-centred radicals show higher chemoselectivity, reducing only the iodide under the reaction conditions. Syringe-pump addition of EPHP can improve the yields of slower cyclisation reactions.

Acknowledgements

We thank the EPSRC and the EU COST D12 initiative for funding and EPSRC Mass Spectrometry Service, Swansea, for high resolution mass spectra. We are grateful to the Ministerio de Educacion y Ciencia (Spain) for a Fellowship to C.G.M.

References

1. Renaud, P.; Lacote, E.; Quaranta, L. *Tetrahedron Lett*. **1998**, *39*, 2123. Crich, D.; Sun, S. *J. Org. Chem*. **1996**, *61*, 7200. Curran, D. P.; Chang, C. T. *J. Org. Chem*. **1989**, *54*, 3140. Barton, D. H. R.; Motherwell, W. B.; Stange, A. *Synthesis* **1981**, 743. Berge, J. M.; Roberts, S. M. *Synthesis* **1979**, 471. Leibner, J. E.; Jacobus, J. *J. Org. Chem*. **1979**, *44*, 449. Corey, E. J.; Suggs, J. W. *J. Org. Chem*. **1975**, *40*, 2554.
2. Curran, D. P.; Hadida, S.; Kim, S. Y.; Luo, Z. Y. *J. Am. Chem. Soc*. **1999**, *121*, 6607. Clive, D. L. J.; Yang, W. *J. Org. Chem*. **1995**, *60*, 2607. Rai, R.; Collum, D. B. *Tetrahedron Lett*. **1994**, *35*, 6221. Vedejs, E.; Duncan, S. M.; Haight, A. R. *J. Org. Chem*. **1993**, *58*, 3046. Light, J.; Breslow, R. *Tetrahedron Lett*. **1990**, *31*, 2857.
3. For a review, see: Walton, J. C.; Baguley, P. A. *Angew. Chem., Int. Ed*. **1998**, *37*, 3072.
4. For some of the many examples, see: Gilbert, B. C.; Kalz, W.; Lindsay, C. I.; McGrail, P. T.; Parsons, A. F.; Whittaker, D. T. E. *Tetrahedron Lett*. **1999**, *40*, 6095. Cassayre, J.; Zard, S. Z. *Synlett* **1999**, 501. Boivin, J.; Pothier, J.; Zard, S. Z. *Tetrahedron Lett*. **1999**, *40*, 3701. Ollivier, C.; Chuard, R.; Renaud, P. *Synlett* **1999**, 807. Devin, P.; Fensterbank, L.; Malacria, M. *Tetrahedron Lett*. **1999**, *40*, 5511. Clark, A. J.; Duncalf, D. J.; Filik, R. P.; Haddleton, D. M.; Thomas, G. H.; Wongtap, H. *Tetrahedron Lett*. **1999**, *40*, 3807. Graham, S. R.; Murphy J. A.; Coates, D. *Tetrahedron Lett.* **1999**, *40*, 2415. Booker-Milburn, K. I.; Barker, A.; Brailsford, W.; Cox, B.; Mansley, T. E. *Tetrahedron* **1998**, *54*, 15321. Molander, G. A.; Harris, C. R. *Chem. Rev*. **1996**, *96*, 307. Baldovini, N.; Bertrand, M.-P.; Carrière, A.; Nouguier, R.; Plancher, J.-M. *J. Org. Chem*. **1996**, *61*, 3205. Binmore, G.; Walton, J. C.; Cardellini, L. *J. Chem. Soc., Chem. Commun*. **1995**, 27. Rajanbabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc*. **1994**, *116*, 986. Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *J. Org. Chem*. **1993**, *58*, 6838. Snider, B. B.; Zhang, Q. *J. Org. Chem*., **1993**, *58*, 3185. Chatgilialoglu, C. *Acc.Chem. Res*. **1992**, *25*, 188. Ali, A.; Harrowven, D.; Pattenden, G. *Tetrahedron Lett*. **1992**, *33*, 2851. Cole, S. J.; Kirwan, J. N.; Roberts, B. P.; Willis, C. R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 103. Fontana, F.; Minisci, F.; Vismara, E. *Tetrahedron Lett.* **1988**, *29*, 1975. Hayes, T. K.; Villani, R.; Weinreb, S. M. *J. Am. Chem. Soc*. **1988**, *110*, 5533.
5. Fletcher, R.; Kizil, M.; Lampard, C.; Murphy, J. A.; Roome, S. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2341. Lampard, C.; Murphy, J. A.; Lewis, N. *J. Chem. Soc., Chem. Commun.* **1993**, 295. Callaghan, O.; Lampard, C.; Kennedy, A. R.; Murphy, J. A. *Tetrahedron Lett*. **1999**, *40*, 161; Callaghan, O.; Lampard, C.; Kennedy, A. R.; Murphy, J. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 995.
6. Graham, S. R.; Murphy, J. A. European Patent Application No. 98115971.8. Graham, S. R.; Murphy, J. A.; Coates, D. *Tetrahedron Lett*. **1999**, *40*, 2415. Graham, S. R.; Murphy, J. A.; Kennedy, A. R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3071.
7. Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron Lett*. **1992**, *33*, 5709. Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *J. Org. Chem*. **1993**, *58*, 6839.
8. Jang, D. O. *Tetrahedron Lett*. **1996**, *37*, 5367.
9. Calderon, J. M. B.; Chicharro, G. J.; Fiandorn, R. J.; Huss, S.; Ward, R. A. 97-EP02284 970506. McCague, R.; Pritchard, R. G.; Stoodley, R. J.; Williamson, D. S. *Chem. Commun*. **1998**, 2691. Tokuyama, H.; Yamashita, T.; Reding, M. T.; Kaburagi, Y.; Fukuyama, T. *J. Am. Chem. Soc*. **1999**, *121*, 3791. Reding, M. T.; Fukuyama, T. *Org. Lett*. **1999**, *1*, 973.
10. This is surprising in view of the seemingly contrary results of Beckwith and Gara with similar cyclisations. However, their work featured an *N*-methyl (as opposed to *N*-mesyl) substituted substrate, and cyclisation onto allyl and butenyl groups as opposed to the cyclohexenyl groups seen here: Beckwith, A. L. J.; Gara, W. B. *J. Chem. Soc., Perkin Trans. 2* **1975**, 796.