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Diethylphosphine Oxide (DEPO): High-Yielding and Facile Preparation of Indolones in Water

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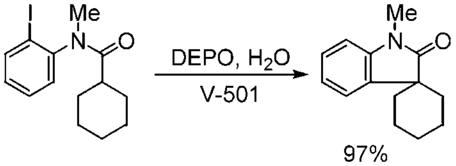
ABSTRACT



Indolones are prepared in excellent yield at 80 °C in water by radical reaction (aryl radical formation, hydrogen atom abstraction, cyclization, and rearomatization) mediated by the reagent diethylphosphine oxide (DEPO). The reaction features V-501 as a water-soluble initiator; no other additives are needed. The process proceeds at a much lower temperature than is required for efficient reaction with toxic tributyltin hydride in benzene and permits significantly higher isolated yields than the corresponding reaction mediated by ethylpiperidine hypophosphite (EPHP).

The drive for new reagents to effect clean carbon−carbon bond formation by radical reactions stems from the well-known problems with the widely used organotin hydrides, notably tributyltin hydride (TBTH), which are neurotoxic. Organotin residues are also noted for difficulties in separation from desired reaction products. Although numerous methods continue to be devised for facilitating separation, thereby diminishing the amounts of tin residues,[1] even traces of tin byproducts pose problems for pharmaceutical manufacture. Perhaps the most popular alternative reagent is tristrimethylsilylsilane,[2] TTMSS, which has a similar, but not identical, range of reactivity to the tin reagent; however, it is much more costly.

Among the newly developed replacement reagents for TBTH, phosphorus compounds,[3,4] particularly hypophosphorous acid and its salts, are receiving considerable attention. These reagents are economical and can be used in water (hypophosphorous acid, usually with an inorganic base) or in organic solvents (the lipophilic salt, *N*-ethylpiperidinium hypophosphite, EPHP),[3,4] and, on workup, separation of neutral organic reaction products is easily achieved by acid- and base-wash.

Initial studies in this area used organic solvents such as benzene and toluene. Jang first showed[3b] that iodoarenecarboxylate salts could be deiodinated by hypophosphorous acid in alkaline aqueous solution, and we showed[3e] using aqueous base that such substrates could be used for C−C bond formation in water. However, important extensions of this chemistry to substrates that are *not* water-soluble (unlike the carboxylate described above) were made by Oshima and coworkers[3i] (EtOH/H_2O in the presence of base) and Kita et al. (H_2O + phase-transfer agent).[3m] The phosphorus reagents are economical and therefore can be used in excess, but this brings a problem in terms of waste, unless the unused phosphorus reagent can be recovered. So far, to our knowledge, this issue has not been addressed. On reaction with an iodo-containing substrate, hypophosphorous acid and

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[1] See: Clive, D. L.J.; Wang, J. *J. Org. Chem.* **2002**, *67*, 1192 and extensive references therein for amelioration of the tin problem and for a full listing of alternate reagents.

[2] (a) Chatgilialoglu, C.; Griller, D.; Lesage, M. *J. Org. Chem.* **1988**, *53*, 3641. (b) Kulicke, K. J.; Giese, B. *Synlett* **1990**, 91. (c) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188.

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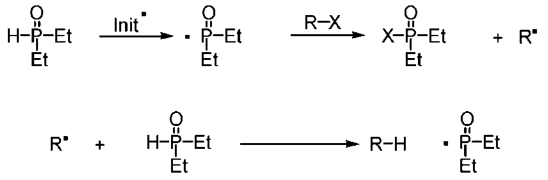
EPHP can form two possible byproducts, IPH(O)(OH) and $I_2P(O)(OH)$; in turn, these can be hydrolyzed to phosphorous acid and phosphoric acid, respectively. Separation of any of these four byproducts from each other or from residual hypophosphorous acid is not trivial, since they are all relatively strong acids.[5]

Recently, our efforts have been directed at finding even simpler procedures for radical reactions using phosphorus radicals. The main purpose of the phase-transfer reagent used in Kita's work is to lead to a greater interaction between the water-soluble phosphorus reagent and the water-insoluble lipophilic substrate. Since the economical phosphorus reagents are normally used in 10−20-fold excess, we wondered whether a phosphorus reagent that is more lipophilic than hypophosphorous acid but still totally soluble in water might avoid the need for the phase-transfer agent. Toward this end, we were attracted by the phosphine oxides, $R_2P(O)H$.

The solubilities of four phosphine oxide examples $R_2P(O)H$ [R = Me, Et, *n*-Bu, and Ph] were screened, and this showed that diethylphosphine oxide (DEPO) had the best profile, dissolving fully in water and in many organic solvents (e.g., DCM, acetone, but being only sparingly soluble in diethyl ether). DEPO was also chosen in preference to dimethylphosphine oxide because DEPO has a higher decomposition temperature.[6] DEPO is easily and economically prepared by addition of ethylmagnesium bromide to diethyl phosphite. Importantly, DEPO[7] has $pK_a = 6$, and so qualifies as an almost neutral compound, but yet would be sufficiently acidic to be extracted into base during workup.

By analogy with other P−H-containing phosphorus compounds, DEPO should react as shown in Scheme 1. We first examined the reduction of *p*-iodoanisole under a range of conditions; in particular, we examined initiation with AIBN, VA-086, V-50, V-501, di-*tert*-butylperoxide, and Et_3B/O_2. From these preliminary studies, V-501 was singled out as the initiator of choice and 80 °C as a convenient temperature for the reduction. This initiator[8] has a half-life of 10 h at 69 °C in water and, being a carboxylic acid, dissolves in water at alkaline pH, and both it and its byproducts can therefore be easily separated from neutral organic compounds by base-wash. At the end of the reaction, diethyl ether was added, and the aqueous phase was made basic (2 M NaOH). Importantly, DEPO (as its salt) remained in the basic aqueous layer, while the desired product was extracted into the ether layer, which was dried and evaporated to afford pure product directly.

Scheme 1



The expected phosphorus byproduct of the reaction, diethylphosphinyl iodide, must undergo rapid hydrolysis under the basic workup conditions, as it was not detected in NMR spectra of the evaporated ethereal layer containing our reaction product.

To screen this reagent, DEPO, we now chose a reaction that is important in our work[9] on alkaloid synthesis, i.e., the conversion of iodoarenes **1** to indolones **2**. This indolone-forming sequence of reactions had previously been successfully carried out with tributyltin hydride[10] but was successful only at elevated temperatures (160 °C; see below). At 80 °C, the bromide analogue of **1a** gave a 20:80 ratio of **2a**:**3a** as judged by GC[10]. The higher temperatures were required because at 80 °C in benzene, abstraction of a hydrogen atom from TBTH is relatively easy compared to cyclization onto the aromatic ring.

Our first efforts used *N*-ethylpiperidine hypophosphite (EPHP) and led to the outcomes shown in column 3 of Table 1. The crude reaction mixtures appeared to contain three aromatic compounds, unreacted **1**, product **2**, and byproduct **3**, as expected. It is seen that considerable amounts of

Table 1. Yields of Cyclized Oxindoles **2** (and Reduced Byproducts **3**) Prepared from Iodoaryl Precursors **1** at 80 °C in Water

substrate	DEPO **2** (%)	EPHP **2**/**3** (%)
1a	97	58/21
1b	90	49/21
1c	87	51/23
1d	82	38/12

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(3) (a) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. Cs. *Tetrahedron Lett.* **1992**, *33*, 5709. (b) Jang, D. O. *Tetrahedron Lett.* **1996**, *37*, 5367. (c) Calderon, J. M. B.; Chicharro, G. J.; Fiandorn, R. J.; Huss, S.; Ward, R. A. EP2284 970506, 1997. (d) McCague, R.; Pritchard, R. G.; Stoodley, R. J.; Williamson, D. S. *Chem. Commun.* **1998**, 2691. (e) Graham, S. R.; Murphy, J. A.; Coates, D. *Tetrahedron Lett.* **1999**, *40*, 2415. (f) Graham, S. R.; Murphy, J. A.; Kennedy, A. R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3071. (g) Tokuyama, H.; Yamashita, T.; Reding, M. T.; Kaburagi, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 3791. (h) Martin, C. G.; Murphy, J. A.; Smith, C. R. *Tetrahedron Lett.* **2000**, *41*, 1833. (i) Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Chem. Lett.* **2000**, 104. (j) Graham, A. E.; Thomas, A. V.; Yang, R. *J. Org. Chem.* **2000**, *657*, 2583. (k) Marotta, E.; Righi, P.; Rosini, G. *Org. Lett.* **2000**, *2*, 4145. (l) Jang, D. O.; Cho, D. H.; Chung, C.-M. *Synlett* **2001**, 1923. (m) Kita, Y.; Nambu, H.; Ramesh, N. G.; Anilkumar, G.; Matsugi, M. *Org. Lett.* **2001**, *3*, 1157. (n) Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 225. (o) Deprele, S.; Montchamp, J. L. *J. Org. Chem.* **2001**, *66*, 6745. (p) Jang, D. O.; Cho, D. H. *Synlett* **2002**, 631. (q) Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Synlett* **2002**, 674. (r) Jang, D. O.; Cho, D. H. *Synlett* **2002**, 1523. (s) Jang, D. O.; Cho, D. H. *Tetrahedron Lett.* **2002**, *43*, 5921. (t) Lee, E., Han, H. O. *Tetrahedron Lett.* **2002**, *43*, 7295. (u) Roy, S. C.; Guin, C.; Rana, K. K.; Maiti, G. *Tetrahedron* **2002**, *58*, 2435. (v) Dubert, O.; Gautier, A.; Condamine, E.; Piettre, S. R. *Org. Lett.* **2002**, *4*, 359. (w) Reding, M. T.; Kaburagi, Y.; Tokuyama, H.; Fukuyama, T. *Heterocycles*, **2002**, *56*, 313. (x) Takamatsu, S. Katayama, S.; Hirose, N.; Naito, M.; Izawa, K. *Tetrahedron Lett.* **2001**, *42*, 7605. (y) Cho, D. H.; Jang, D. O. *Bull. Korean Chem. Soc.* **2003**, *24*, 15. (z) Nambu, H.; Anilkumar, G.; Matsugi, M.; Kita, Y. *Tetrahedron* **2003**, *59*, 77.

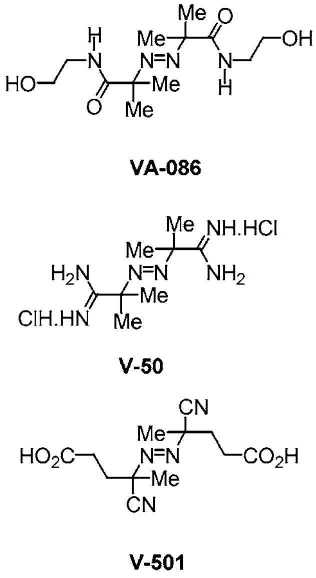
(4) For other radical reagents based on phosphorus, see: (a) Barks, J. M.; Gilbert, B. C.; Parsons, A. F.; Upeandran, B. *Tetrahedron Lett.* **2001**, *42*, 3137. (b) Jessop, C. M.; Parsons, A. F.; Routledge, A.; Irvine, D. *Tetrahedron Lett.* **2003**, *44*, 479. **(**c) Jang, D. O.; Cho, D. O.; Barton, D. H. R. *Synlett* **1998**, 39.

(5) pK_a values: H_3PO_2, 1.3; H_3PO_3, 1.3 and 6.78; H_3PO_4, 2.15, 7.20, and 12.38. http://www.swbic.org/education/env-engr/chem/acidconstants.html.

(6) Hays, H. R. *J. Org. Chem.* **1968**, *33*, 3690

(7) Determined using a Jenny 3015 pH meter at 25 °C.

Scheme 2

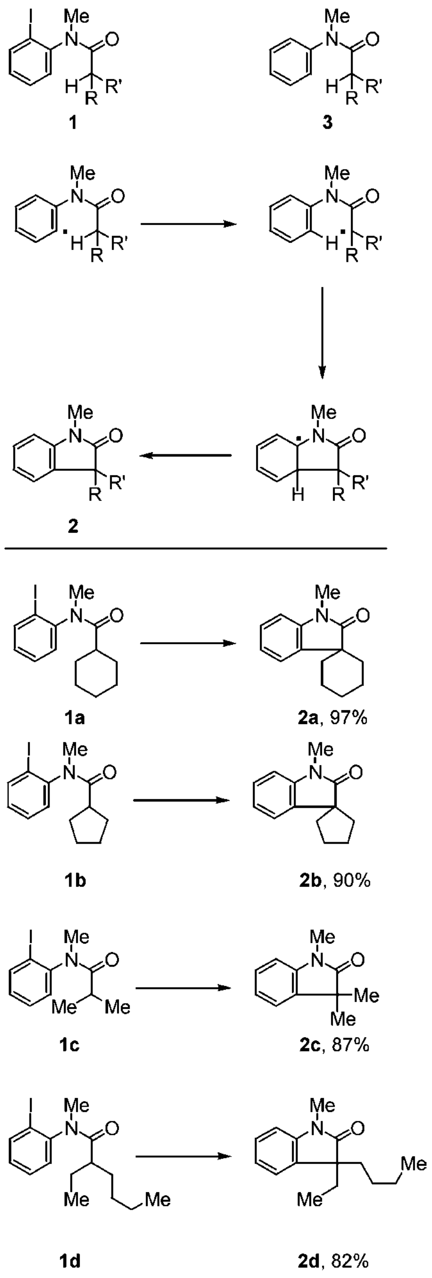


reduced compounds **3** are formed, although the ratios are better than for TBTH at the same temperature. However, the mass balances on *isolated* compounds were not always good, and we established that this was due to the volatility of the indolones during evaporation of the toluene solvent. Since the indolones are not expected to have low boiling points (compound **1a** has a boiling point of 180 °C @ 19 mm Hg),[11] we can only ascribe this unexpected loss to an azeotropic effect.

The preparation and isolation in high yield of these compounds therefore posed a problem, but we reasoned that they should provide an excellent test for the DEPO protocol, involving workup with diethyl ether; substrates **1a**−**d** were therefore tested (see Supporting Information). As seen in Scheme 3, the reactions proceed in excellent yield, and the workup directly affords products that are essentially pure. The most interesting findings, however, were related to the product profile. When EPHP had been used as a reagent, significant quantities of reduced compounds **3** were obtained, while with DEPO, no reduced compound was observed with **1a** and very minute quantities with **1b**−**d**. This shows clearly that DEPO is a superior reagent for this transformation. However, DEPO has another advantage over EPHP in that the byproduct, diethylphosphinyl iodide, is easily converted to diethylphosphinic acid (pK_a = 3.29)[12] and separation of this product from residual DEPO (pK_a = 6.0) is easily accomplished by adjusting the pH to 5.0.

When compared with tributyltin hydride (TBTH), DEPO also proves to be a better reagent as (quite aside from issues of cost and toxicity) temperatures of 160 °C were required with TBTH to obtain good yields of cyclized products.

Scheme 3



Having established that DEPO is very useful for indolone formation, we were keen to investigate whether it would be equally successful for other radical reactions. The key reaction for routine radical cyclizations is cleavage of C−I and C−Br bonds, and as seen above, this is readily achieved by DEPO. However, phosphorus radicals also readily add to alkenes[4,3n,u]; if this occurs more rapidly than C−I cleavage, then the reagent would have limited value. To test this, the iodoarenes, **4a**−**c** and **6a**−**c**, were prepared and treated with DEPO in water at 80 °C. As above, the reactions were relatively slow (4 days, 20 equiv of DEPO and 0.37 equiv of V-501 each 12 h). As seen in Scheme 4, this provided

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(8) Yorimitsu, H.; Wakabayashi, K.; Shinkubo, H.; Oshima, K. *Tetrahedron Lett.* **1999**, *40*, 519.

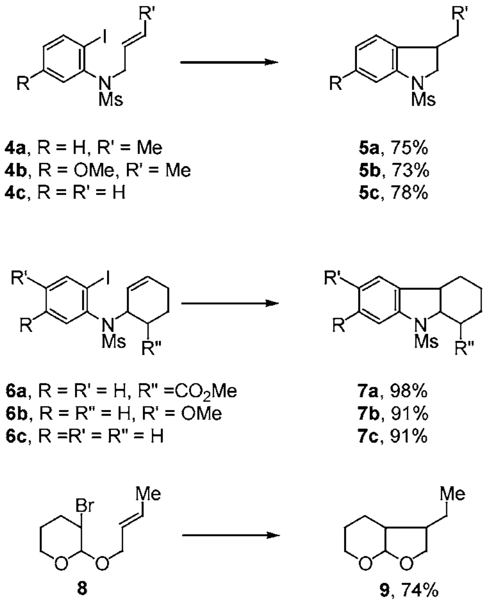
(9) (a) Lizos, D. E.; Murphy, J. A. *Org Biomol. Chem.* **2003**, *1*, 117. (b) Lizos, D.; Tripoli, R.; Murphy, J. A. *Chem. Commun.* **2001**, 2732.

(10) (a) Beckwith, A. L. J.; Storey, J. M. D. *J. Chem. Soc., Chem. Commun.* **1995**, 977. (b) Storey, J. M. D. *Tetrahedron Lett.* **2000**, *41*, 8173.

(11) Gibson, M. S. *J. Chem. Soc.* **1961**, 2249.

(12) Crofts, P. C.; Kosolapoff, G. M. *J. Am. Chem. Soc.* **1953**, *75*, 3379.

Scheme 4



the desired products in very good yields. We were particularly keen to compare the terminal alkene case, **4c**, with more highly substituted alkenes **4a**,**b**, since terminal alkenes can show particular sensitivity to phosphorus radical addition.[4] The similarity of the yields of isolated products from **4a**−**c** suggests that this is not a problem.

Finally, we tested the reagent with the acid-sensitive aliphatic bromide **8** (10 equiv of DEPO, 0.5 equiv of V-501, 12 h). Again, this gave very good yield of the cyclized product **9** and no evidence of acetal hydrolysis was seen.

In summary, the first examples of indolone formation using phosphorus reagents are reported. DEPO is introduced as a reagent that can work in water with no need for additives (only initiator, substrate, and water are needed). This reagent affords extremely easy workup and affords high yields of product, free from phosphorus or initiator-derived byproducts.

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Supporting Information Available: Methods of preparation as well as spectroscopic data for compounds **2a**−**d**, **5a**−**c**, **7a**−**c**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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