ORGANIC LETTERS

2003
Vol. 5, No. 22
4187−4190

Improved Reagent for Electrophilic Amination of Stabilized Carbanions

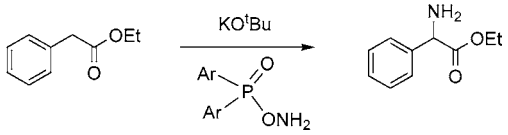
Jason A. Smulik and Edwin Vedejs*

Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109

edved@umich.edu

Received August 27, 2003

ABSTRACT



Enolate amination using *O*-di(*p*-methoxyphenyl)phosphinylhydroxylamine 2 is reported. Reagent 2 reacts efficiently with stabilized sodium or potassium enolates derived from malonates, phenylacetates, and phenylacetonitriles and is sufficiently soluble for use in solution at −78 °C.

Direct amination of carbanions has been described using a variety of hydroxylamines as electrophilic NH_2^+ equivalents,[1] including *O*-diarylphosphinyl-,[2] *O*-acyl,[3] *O*-sulfonyl,[4] and *O*-dinitrophenyl derivatives,[5] and a variety of *O*-alkyl hydroxylamines.[6] The diphenylphosphinyl reagent **1**[2a] has the most extensive track record for aminations[2b,c] and works moderately well with a range of Grignard reagents and somewhat better with increasingly stabilized enolates. However, the enolate aminations are less predictable for more basic enolates, a pattern that has also been noted using *O*-2,4-dinitrophenyl-hydroxylamine.[5a]

Compared to the other activated hydroxylamines, **1** has the best reputation for stability, and the solid reagent may be stored for extended periods. Unfortunately, improved stability appears to reflect crystal lattice issues and comes at the price of minimal solubility in nonpolar solvents, a factor that may limit the reactivity of **1**. A literature precedent recommends stirring stabilized lithium enolates with a suspension of **1** for 12 h at room temperature to achieve aminations.[2b] These conditions would not be compatible with potential applications of interest in our laboratory where the need to conduct aminations −78 °C was anticipated.

Upon perusal of the literature, we noticed that Harger had reported the di(*p*-dimethoxyphenyl)phosphinylhydroxylamine **2** in the same paper that first deduced the correct structure of reagent **1**.[2a] To our knowledge, **2** has not been used for aminations, although one might expect improved solubility in view of Harger's isolation method (crystallization from chloroform/ether or ethanol/ether) and from the lower melting point compared to that of **1**. In this report, we demonstrate that reagent **2** is indeed more soluble and is sufficiently reactive for use in electrophilic amination of stabilized carbanions at −78 °C. We also provide comparisons with *O*-(*p*-nitrobenzoyl)hydroxylamine **3**, a reagent that has been

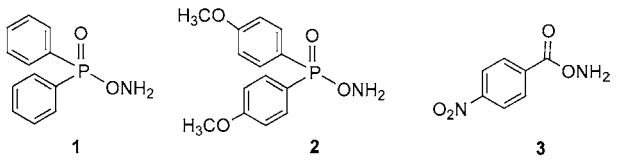


Figure 1. Electrophilic aminating reagents **1**−**3**.

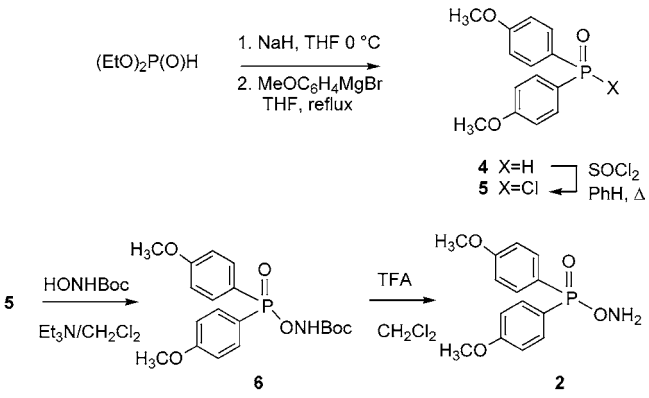
(1) Review: Erdik, E.; Ay, M. *Chem. Rev.* **1989**, *89*, 1947.
(2) (a) Harger, M. J. P. *J. Chem. Soc., Perkin Trans. 1* **1981**, 3284. (b) Boche, G.; Bernheim, M.; Schott, W. *Tetrahedron Lett.* **1982**, *23*, 5399. (c) Colvin, E. W.; Kirby, G. W.; Wilson, A. C. *Tetrahedron Lett.* **1982**, *23*, 3835. (d) Boche, G. *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; Vol. 4, p 2240. (e) Klötzer, W.; Stadlwieser, J.; Raneburger, J. *Org. Synth.* **1986**, *64*, 96.
(3) (a) Carpino, L. A. *J. Am. Chem. Soc.* **1960**, *82*, 3133. (b) Marmer, W. N.; Maerker, G. *J. Org. Chem.* **1972**, *37*, 3520. (c) Boche, G. *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; Vol. 5, p 3270. (d) Shen, Y.; Friestad, G. K. *J. Org. Chem.* **2002**, *67*, 6236.
(4) (a) Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1. (b) Taylor, E. C.; Sun, J.-H. *Synthesis* **1980**, 801.
(5) (a) Radhakrishna, A. S.; Loudon, G. M.; Miller, M. J. *J. Org. Chem.* **1979**, *44*, 4836. (b) Belletini, J. R.; Olson, E. R.; Teng, M.; Miller, M. J. *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed., Wiley: New York, 1995; Vol. 3, p 2189.
(6) Oguri, T.; Shioiri, T.; Yamada, S. *Chem. Pharm. Bull.* **1975**, *23*, 173.

10.1021/ol035629w CCC: $25.00
Published on Web 10/10/2003

recommended for amination of amide anions[3d] but has not been tested for amination of enolates.

Reagents **1** and **2** have been prepared from the corresponding diarylphosphinic chlorides and hydroxylamine.[2a,e] In our hands, preparation of **1** on gram scale using this method gave inconsistent results in aminations as a result of batch-dependent variations in purity. There were also concerns with the literature procedure to prepare **2** because the crystallization step involves ethanol or chloroform,[2a] solvents that would have to be removed prior to amination of increasingly basic enolates. We prefer an alternative synthesis of **2** (Scheme 1) using N-protected hydroxylamine.

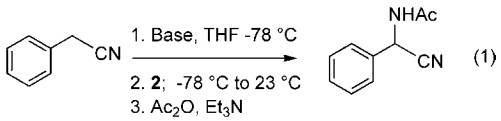
Scheme 1. Synthesis of **2**



The method involves one more step than the Harger synthesis, but it is straightforward and provides **2** in sufficient purity for convenient use.[7]

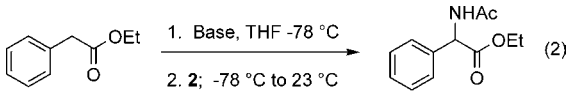
Preparation of aminating reagent **2** was performed via the known diarylphosphinous acid **4**[8] (Scheme 1). Conversion to the corresponding diarylphosphinic chloride **5** with thionyl chloride, followed by HONHBoc/Et_3N gave **6**. Cleavage of the Boc-protecting group with TFA afforded **2** in 50% yield overall from the phosphinous acid **4**. After workup, **2** was easily isolated by precipitation of the crude solid from a minimal amount of CH_2Cl_2 with hexane. This material has a single phosphorus resonance in the ^{31}P NMR spectrum and is sufficiently pure for use with typical stabilized carbanions as described below. Reagent **2** has been reported to decompose at ambient temperature,[2a] but no appreciable decomposition or loss of activity was found upon storing the dry solid at −20 °C over several months. The electrophilic amination of phenylacetonitrile using **2** was evaluated using lithium, sodium, and potassium bases for anion generation (Table 1). Boche had reported the same amination using LDA and **1** as the reagent and had obtained the aminonitrile in 37% yield (anion formation and addition of **1** at −78 °C; amination at room temperature).[2b] Following a similar procedure, reagent **2** gave better conversions and isolated yields using all three bases examined (Table 1), with the best result obtained with KO^{t}Bu (67%). Somewhat different results were obtained in the electrophilic amination of ethyl phenylacetate using **2** and various bases (Table 2; product assay after conversion to the acetamide). Lithium enolates gave significantly lower yields of the aminated product (entries 1 and 2), but increased conversion was found for sodium and potassium enolates (entries 3 and 4).[9] Metal-free enolate generation was also briefly examined using the P_2-^{t}Bu phosphazine base,[10] but this procedure gave a low yield in the amination (entry 4).

Table 1. Phenylacetonitrile Amination; **2** with Li, Na, and K Bases



entry	base	conversion (%)
1	LiHMDS	59
2	NaHMDS	64
3	KO^{t}Bu	67

Table 2. Ethyl Phenyl acetate Amination with **2** versus Bases

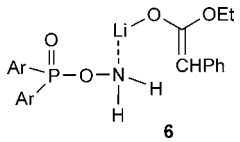


entry	base	conversion (%)
1	LiHMDS	22
2	LDA	31
3	NaHMDS	46
4	KO^{t}Bu	67
5	P_2-^{t}Bu	25

(7) ***O*-(Di-*p*-methoxyphenyl)phosphinylhydroxylamine.** In a flame-dried flask equipped with magnetic stir bar and reflux condenser was dissolved 1.0 g (3.81 mmol, 1.0 equiv) of di(*p*-methoxyphenyl)phosphinous acid[8] in 8.0 mL of benzene. The solution was cooled to 0 °C, and 0.42 mL (5.72 mmol, 1.5 equiv) of $SOCl_2$ was added dropwise via syringe. The flask was then transferred to an 80 °C oil bath and stirred for 2 h. The solution was concentrated (aspirator) to yield the diarylphosphinic chloride as a yellow oil that was used in the next step. In a 100-mL round-bottom flask equipped with a magnetic stir bar were dissolved 0.510 g (3.81 mmol, 1.0 equiv) of HONHBoc and 0.80 mL (5.72 mmol, 1.5 equiv) of Et_3N in CH_2Cl_2 (40 mL), and the mixture was cooled to 0 °C. To this solution was added the di(*p*-methoxyphenyl)phosphinic acid chloride in CH_2Cl_2 (4.0 mL) via syringe in one portion. The solution was allowed to warm to 23 °C. After stirring for 8 h, CH_2Cl_2 (50 mL) and H_2O (100 mL) were added, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The CH_2Cl_2 extract was dried ($MgSO_4$), filtered, and concentrated, and the crude oil was purified by flash chromatography (1:1 EtOAc/hexane) to give 1.05 g (70%) of **6** as a white solid. Analytical TLC: R_f 0.15 (1:1 ethyl acetate/hexanes). The white solid was dissolved in CH_2Cl_2 (4 mL), and TFA (4 mL) was added in one portion at 23 °C. After stirring for 30 min, the solution was diluted with CH_2Cl_2 (30 mL) and H_2O (30 mL) and solid $NaHCO_3$ was added until gas evolution had ceased. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was dissolved in CH_2Cl_2 (4.0 mL), and hexane (50 mL) was slowly added to yield 0.55 g (71%) of **2** as a finely divided white solid that was collected by filtration (rt) and dried under vacuum (0.5 h). ^{31}P NMR (162 MHz, $CDCl_3$) δ 39.6 ppm.

(8) Kanai, M.; Nakagawa, Y.; Tomioka, K. *Tetrahedron* **1999**, *55*, 3843.

Lower conversion in the phenylacetate lithium enolate aminations implicates competing proton transfer from the reagent **2** to quench the enolate. One possibility is internal proton transfer in the complex **6**, a scenario that is reminis-



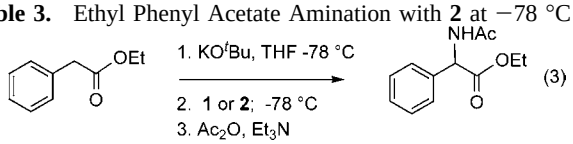
6

cent of the internal proton return phenomenon observed in reactions of amine-containing lithium enolates with other electrophiles.[11] Simple intermolecular proton transfer is not ruled out, but the internal pathway would be consistent with the higher conversions observed for enolates containing the less Lewis acidic sodium or potassium ions.

The prospects for simple proton transfer from the reagent **2** to the ester enolate depend on the relative acidities in THF, as well as on kinetic factors. Values for pK_a's in the range of 22−24[12] for phenylacetate ester or phenylacetonitrile anions have been reported, but little is known about O-substituted hydroxylamine pK_a's in organic solvents. The closest analogy (PhNHOBn; DMSO pK_a = 23.5)[13] provides some indication that proton transfer from **2** to the enolate may be possible. Furthermore, prior studies using *O*-(2,4-dinitrophenyl)hydroxylamine had found evidence for N−H deprotonation by the lithium enolate of methyl phenylpropionate,[5a] followed by self-amination of the reagent and fragmentation to diimide.[14] From **2**, the analogous decomposition process would lead to $Ar_2P(O)OH$, a product that was detected by ESMS in partly decomposed samples of **2** and was also noted in the original report describing the synthesis of **1** and **2**.[2a]

To establish temperature and reactivity limits, the electrophilic amination of ethyl phenylacetate/KO^{t}Bu using reagent **2** was explored at −78 °C (Table 3). Reactions conducted at 0.10 M resulted in heterogeneous mixtures and ca. 30% product formation after 2 h. When sufficient THF was added to dissolve the reagent **2** (ca. 0.01 M), improved conversions were found if sufficient time was allowed to compensate for high dilution in the second-order amination step (entries 1 and 2).

Table 3. Ethyl Phenyl Acetate Amination with **2** at −78 °C



entry	reagent	time (h)	conversion (%)	additive	concn (M)
1	**2**	2	35	none	0.01
2	**2**	6	76	none	0.01
3	**2**	2	44	DMF	0.05
4	**2**	6	55	DMF	0.05
5	**2**	2	57	CH_2Cl_2	0.05
6	**2**	4	70	CH_2Cl_2	0.05
7	**1**	6	27	none	0.01

Other solvents were investigated to improve solubility. Reagent **2** was found to be readily soluble in DMF, but aminations conducted using 1.1 equiv of **2** with DMF as a cosolvent in THF at −78 °C gave lower conversions even though the conditions were homogeneous (entries 3 and 4). On the other hand, addition of ca. 33% CH_2Cl_2 resulted in good conversion and a faster reaction at 0.05 M. For comparison, low-temperature electrophilic amination was also attempted using reagent **1**. Although reaction mixtures remained heterogeneous (0.01 M) at −78 °C using **1**, some conversion to product was observed (Table 3, entry 7). These findings suggest that there is little intrinsic reactivity difference between **1** and **2** and that the substantial differences in % conversion reflect differences in the rate of self-destruction compared to amination for reagent in solution (**2**) or suspension (**1**).

Having established that **2** is suitable for low-temperature aminations of the stabilized phenylacetate enolate, we compared **2** with the original reagent **1** under simple room-temperature amination conditions (Table 4; ca. 0.1 M, heterogeneous conditions). Similar conditions had been used by Boche et al., although the latter workers used LDA as the base,[2b] whereas our experiments were conducted using KO^{t}Bu or NaH. Table 4 summarizes representative aminations of malonates, phenylacetates, and phenylacetonitriles using reagents **2** (column 2) and **3**[3d] (column 3) and also lists literature data obtained with reagent **1** (column 1).[2b,c] Reagent **3** (*O*-(4-nitrobenzoyl)-hydroxylamine) proved to be quite effective for amination of the more highly stabilized enolates and is probably the reagent of choice for this purpose

(9) **Representative Experimental Procedure.** CAUTION! Although we have not experienced, and are not aware of, detonations in the preparation or use of reagents **1**, **2**, or **3**, the related *O*-(mesitylsulfonyl)hydroxylamine is explosive[3a−c] and detonation of *O*-dinitrophenylhydroxylamine in the presence of KH has been reported.[5a] In view of this history, reagents **1**−**3** must be regarded as potential explosives, especially when the solid reagents are mixed with strong base. Into a flame-dried 25-mL flask equipped with a magnetic stir bar was dissolved 41 mg (0.25 mmol, 1.0 equiv) of ethyl phenylacetate in THF (3.0 mL), and the mixture was cooled to −78 °C. A freshly prepared solution of 31 mg (0.28 mmol, 1.1 equiv) of KO^{t}Bu in THF (2.0 mL) was added dropwise via syringe, and the resulting solution was allowed to stir for 15 min at −78 °C. Next, 81 mg (0.28 mmol, 1.1 equiv) of reagent **2** was added in one portion as a solid, and the mixture was slowly allowed to reach 23 °C and stir overnight. To the solution was added 71 μL (0.75 mmol, 3.0 equiv) of Ac_2O and 210 μL (1.5 mmol, 6.0 equiv) of Et_3N sequentially via syringe, and the mixture was allowed to stir an additional 1 h at 23 °C. The solution was diluted with Et_2O (20 mL) and a saturated solution of ammonium chloride (30 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated (rotary evaporator), and the crude oil was purified by flash chromatography (1:1 ethyl acetate/hexanes) to give 37 mg of acetamide (67%) as a colorless oil. Analytical TLC: R_f 0.20 (1:1 ethyl acetate/hexanes).

(10) Schwesinger, R.; Schlemper, H.; Hasenfratz, C.; Willaredt, J.; Dambacher, T.; Breuer, T.; Ottaway, C.; Fletschinger, M.; Boele, J.; Fritz, H.; Putzas, D.; Rotter, H. W.; Bordwell, F. G.; Satish, A. V.; Ji, G.-Z.; Peters, E.-M.; Peters, K.; von Schnering, H. G.; Walz, L. *Liebigs Ann.* **1996**, 1055.

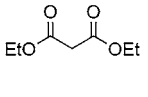
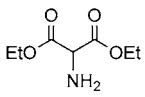
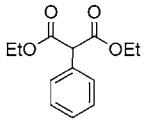
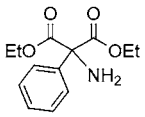
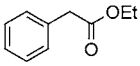
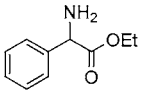
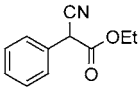
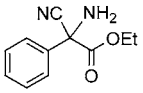
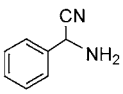
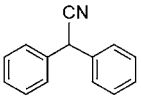
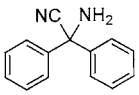
(11) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624.

(12) (a) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456. (b) Kaufman, M. J.; Streitwieser, A. *J. Am. Chem. Soc.* **1987**, *109*, 6092.

(13) Hughes, M. N.; Nicklin, H. G.; Shrimanker, K. *J. Chem. Soc. (A)* **1971**, 3485. Bordwell, F. G.; Liu, W.-Z. *J. Am. Chem. Soc.* **1996**, *118*, 8777.

(14) Diimide formation was deduced from the formation of olefin hydrogenation products; see ref 5a.

Table 4. Scope and Comparison of Aminating Reagents[d]

entry	substrate	product	conditions	1[2b,c]	2	3
1			A	57%[b]	41%[a]	52%[a]
2			A	31%[c]	92%	99%
3			B	45%[c]	67%[a]	<2%
4			A	96%[c]	75%	85%
5			B	37%[c]	64%[a]	10%[a]
6			A	67%[c]	85%	66%

[a] Isolated as the acetamide. [b] Sodium enolate.[2c] [c] Lithium enolate.[2b] [d] Conditions A: NaH/THF, 15 min, 23 °C; **2** or **3**, overnight, 23 °C. Conditions B: KO^{t}Bu/THF, 15 min, −78 °C; **2** or **3**, overnight, 23 °C.

because of its ease of preparation and storage.[3b] However, **3** was not suitable for amination of the more highly basic anions (entries 3 and 5).

Overall, the results for **1** and **2** in Table 4 show an advantage for **2** with the more basic anions. Highly stabilized carbanions were aminated smoothly with either **1** or **2**, and clean conversion was observed using 1.1 equiv of reagent **2** for entries 2, 4, and 6. In these examples, it was experimentally convenient to use NaH/THF (conditions A) to generate the stabilized carbanions, while KO^{t}Bu was necessary for entries 3 and 5.

As the pK_a of the substrate was increased, amination yields decreased (Table 4, entries 3 and 5). Furthermore, attempts to use reagent **3** for the amination of acetophenone enolate were unsuccessful, while **2** gave 4% of the product (isolated as the *N*-acetyl derivative). The pK_a of acetophenone is 24.7 (DMSO),[12a] so this enolate may well be basic enough to deprotonate **2**, resulting in decomposition of the reagent.

The aminations using **2** are improved compared to analogous literature results for **1**.[2b,c] Although the solubility difference between **1** and **2** is not large, it is sufficient to show that the rate of amination at −78 °C is limited by solubility for reagent **1**.

In summary, electrophilic amination conducted using the diarylphosphinylhydroxylamine **2** has been documented. Reagent **2** was reliably prepared on gram scale from diethyl phosphite via the diarylphosphinyl chloride **5**. The best results were obtained with highly stabilized sodium and potassium enolates, but the more basic phenylacetate and phenylacetonitrile anions also gave good yields.

Acknowledgment. This work was supported by the National Institutes of Health (CA17918).

OL035629W