Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 849–851

TETRAHEDRON LETTERS

Condensations of *N*-arylhydroxylamines for the preparation of 5,5′-di-*tert*-butyl-2,2′-dihydroxydiphenylamine

John D. Spence,* Ashley E. Raymond and Dianne E. Norton

Department of Chemistry, Trinity University, 715 Stadium Dr., San Antonio, TX 78212, USA

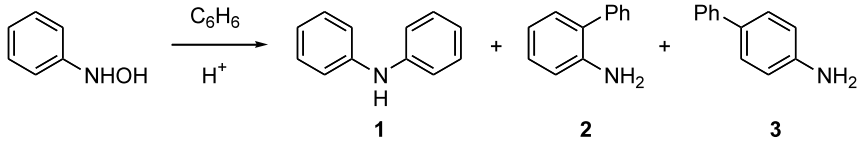
Received 14 October 2002; accepted 19 November 2002

Abstract—Acid-promoted condensation of 4-*tert*-butyl-2-hydroxylaminoanisole with *p*-*tert*-butylphenol resulted in the formation of 5,5′-di-*tert*-butyl-2,2′-dihydroxydiphenylamine upon demethylation with BBr_3. Protection of the acidic phenol unit was required to isolate the acid labile *N*-arylhydroxylamine intermediate.

Macrocyclic oligomers of *p*-*tert*-butylphenol and formaldehyde, commonly referred to as calixarenes, have received widespread interest over the past 30 years.[1] A major factor contributing to the rapid growth in calixarene chemistry can be traced to the ready availability of the major calixarenes via one-step syntheses[2] and the development of fragment syntheses for non-symmetrical systems.[3] Their appeal is further multiplied by the ease of modification along the upper rim *para*-alkyl and lower rim phenolic groups allowing the preparation of a diverse array of macrocycles. Functionalization along the bridge position, however, has received limited attention primarily focused on alkanediyl,[4] thia[5] and the expanded[6] calixarenes. While dihomoazacalixarenes are known[6c] analogs with a direct nitrogen bridge between the aryl units have not been reported due to synthetic difficulties in preparing diarylamines. As part of a building block approach towards the preparation of nitrogen-bridged calixarenes we sought to prepare diphenylamines derived from *p*-*tert*-butylphenol that can be employed in a fragment approach towards the synthesis of azacalixarenes.

Among the methods available for the synthesis of diphenylamines we chose to re-visit the acid-promoted condensation of *N*-arylhydroxylamines with aryl rings. The parent version of this reaction, the condensation of hydroxylaminobenzene with benzene, has been reported to produce a mixture of *N*-substituted diphenylamine **1** and C-substituted biphenylamines **2** and **3** (Scheme 1).[7] Employment of this strategy for the preparation of diarylamines would parallel those used in the fragment syntheses of calixarenes that employ 2-hydroxymethyl or 2-bromomethyl-4-*tert*-butylphenols to incorporate methylene bridges between aryl subunits. Herein we report on the synthesis of an *N*-arylhydroxylamine derived from *p*-*tert*-butylphenol and its acid-promoted condensation to prepare 5,5′-di-*tert*-butyl-2,2′-dihydroxydiphenylamine.

Initial attempts to prepare the desired *N*-arylhydroxylamine by the partial reduction of 4-*tert*-butyl-2-nitrophenol under a variety of conditions resulted in the isolation of 2-amino-4-*tert*-butylphenol due to over reduction. It is well known that *N*-arylhydroxylamines are acid-sensitive[8] and we speculated that the *ortho*-phenol moiety facilitated a dehydration of the hydroxylamine, producing an *o*-benzoquinonimine, which was rapidly reduced to the aminophenol. While reductions of substituted nitrobenzenes to hydroxylamines have

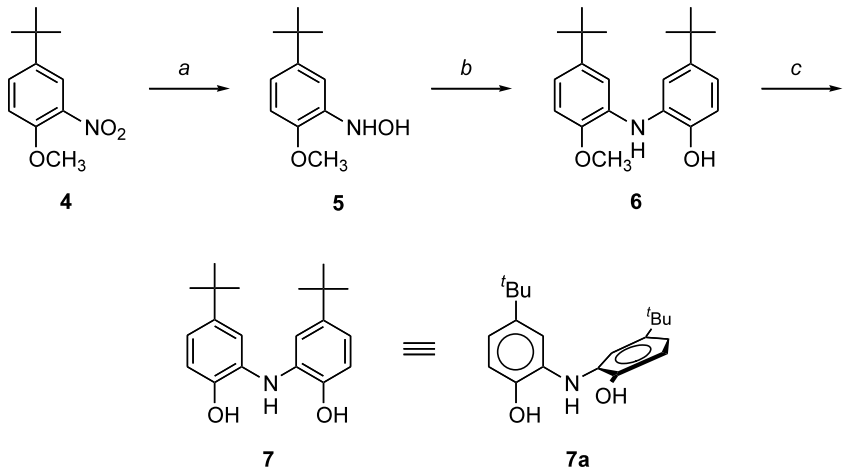


Scheme 1.

Keywords: nitroaromatics; reductions; *N*-arylhydroxylamines; diphenylamines.

* Corresponding author. Tel.: (210) 999-7660; fax: (210) 999-7569; e-mail: john.spence@trinity.edu

0040-4039/03/$ - see front matter
PII: S0040-4039(02)02699-0



Scheme 2. *Reagents and conditions*: (a) H_2NNH_2, Pd/C, THF, 0°C. (b) H^+, *p-tert*-butylphenol, CH_2Cl_2 (two-step yield 13–60%, see Table 1). (c) BBr_3, CH_2Cl_2, 0°C (81%).

Table 1. Condensation of hydroxylamine **5** with *p-tert*-butylphenol[a]

Entry	Acid	Conditions	Diphenylamine **6**[b] (%)
1	TFA	2.5 equiv. acid, 1.0 equiv. *p-tert*-butylphenol	44
2	TsOH	2.5 equiv. acid, 1.0 equiv. *p-tert*-butylphenol	40
3	TFSA	2.5 equiv. acid, 1.0 equiv. *p-tert*-butylphenol	13
4	TFA	10 equiv. acid, 1.0 equiv. *p-tert*-butylphenol	41
5	TFA	2.5 equiv. acid, 5.0 equiv. *p-tert*-butylphenol	60

[a] Reaction conditions 0.1 M **5** in CH_2Cl_2, room temperature, under N_2.
[b] Isolated two-step yield from **4** after purification.

been reported[9] there are no examples describing the synthetic preparation of 2-hydroxylaminophenols. Reduction of anisole **4**, however, under catalytic hydrogen transfer conditions afforded the desired hydroxylamine **5** (Scheme 2) along with a minor amount of 2-amino-4-*tert*-butylanisole (<10%). The hydroxylamine was readily identified by GCMS and ^1H NMR spectroscopy which displayed a characteristic AMX system in the aromatic region along with two exchangeable signals for the N*HOH*. Integration of the well resolved *tert*-butyl or methoxy signals in the crude ^1H NMR spectra indicated an 11:1 ratio favoring hydroxylamine **5** over 2-amino-4-*tert*-butylanisole. Due to the lability of hydroxylamine **5** this mixture could not be separated and the crude reduction product was taken directly into the condensation reaction.

To examine the condensation reaction anisole **4** was reduced on a 5 mmol scale in THF (150 mL) with H_2NNH_2 (4.0 mL) and Pd/C (4.0 g) at 0°C for 2 h. After vacuum filtration and evaporation of the THF the crude yellow oil was dissolved in 50 mL CH_2Cl_2 to prepare a 0.1 M stock solution. 10 mL Aliquots of this stock solution were then immediately subjected to acid-promoted condensation with *p-tert*-butylphenol to optimize formation of diphenylamine **6** (Scheme 2). The reaction conditions examined and two-step yields for the conversion of **4** into **6** are shown in Table 1.

The acid-promoted condensation was initially examined with TFA which has been reported to give the highest yields of diphenylamine **1** in the condensation of hydroxylaminobenzene with benzene (Scheme 1).[7] Upon treatment of **5** with 1 equiv. of *p-tert*-butylphenol in the presence of 2.5 equiv. of TFA in CH_2Cl_2 diphenylamine **6** was obtained as the only condensation product in 44% yield (entry 1). *p*-TsOH, commonly used in calixarene syntheses, was found to behave similarly to TFA (entry 2). Stronger acids such as TFSA, on the other hand, have been reported to produce biphenylamines as major products and resulted in the lowest observed yield of diphenylamine **6** in the present study (entry 3). The presence of the bulky *tert*-butyl substituent directly adjacent to the available C-alkylation sites is apparently large enough to prevent C-substitution as no evidence of biphenylamine products was observed under any conditions studied.[10] The reaction was found to be insensitive to a large excess of acid (entry 4), however, a fivefold excess of *p-tert*-butylphenol increased the overall yield to 60% (entry 5). In each reaction a minor amount of 2-amino-4-*tert*-butylanisole was isolated (6–10%) along with trace amounts of azo and azoxy products. To simplify purification the 2-aminoanisole by-product was removed by extracting with 5% HCl and excess *p-tert*-butylphenol was removed by sublimation prior to column chromatography. In our hands diphenylamine **6** could rou-

tinely be isolated as a tan oil in a 50–60% two-step yield.†

The methyl protecting group in **6** was removed by treatment with BBr_3 at 0°C to afford 5,5′-di-*tert*-butyl-2,2′-dihydroxydiphenylamine **7**‡ in 81% yield after chromatography (Scheme 2). Care must be taken in the demethylation step to avoid removal of the *tert*-butyl substituent which occurred upon warming to room temperature. While diphenylamine **6** is air stable, **7** required storage under nitrogen and rapidly decomposed to a complex mixture of products upon exposure to acid. The ^{1}H NMR spectrum of **7** indicated that the diphenylamine adopts a non-planar conformation (**7a**) in solution whereby the two aryl rings are non-equivalent.[11] The room temperature spectra showed anisochronous signals for the 6,6′-hydrogens at δ 6.61 and 6.15 in DMSO-d_6 along with two singlets for the *tert*-butyl substituents at δ 1.24 and 1.23.

The procedure described here allows the incorporation of nitrogen-bridges between aryl units derived from *para*-substituted phenols and utilization of this condensation strategy for the preparation of aza-bridged calixarenes will be reported elsewhere.

Acknowledgements

This work was funded by grants from the Welch Foundation (W-0031) and the NSF-REU program (CHE-9820176). Mass spectra were obtained at the MSU Mass Spectrometry Facility.

References

1. (a) Gutsche, C. D. In *Calixarenes Revisited*; Stoddart, J. F., Ed.; Monographs in Supramolecular Chemistry No. 6; The Royal Society of Chemistry: Cambridge, 1998; (b) Gutsche, C. D. In *Calixarenes*; Stoddart, J. F., Ed.; Monographs in Supramolecular Chemistry No. 1; The Royal Society of Chemistry: Cambridge, 1989.
2. Gutsche, C. D.; Dhawan, B.; No, K. H.; Muthukrishnan, R. *J. Am. Chem. Soc.* **1981**, *103*, 3782.
3. Böhmer, V.; Merkel, L.; Kunz, U. *J. Chem. Soc., Chem. Commun.* **1987**, 896.
4. (a) Scully, P. A.; Hamilton, T. M.; Bennett, J. L. *Org. Lett.* **2001**, *3*, 2741; (b) Bergamaschi, M.; Bigi, F.; Lanfranchi, M.; Maggi, R.; Pastorio, A.; Pellinghelli, M. A.; Peri, F.; Porta, C.; Sartori, G. *Tetrahedron* **1997**, *53*, 13037; (c) Biali, S. E.; Böhmer, V.; Cohen, S.; Ferguson, G.; Grüttner, C.; Grynszpan, F.; Paulus, E. F.; Thondorf, I.; Vogt, W. *J. Am. Chem. Soc.* **1996**, *118*, 12938.
5. For a review, see: Iki, N.; Miyano, S. *J. Inclusion Phenom. Macrocycl. Chem.* **2001**, *41*, 99.
6. (a) For homocalixarenes, see: Ibach, S.; Prautzsch, V.; Vögtle, F.; Chartroux, C.; Gloe, K. *Acc. Chem. Res.* **1999**, *32*, 729; (b) For dihomooxacalixarene, see: Dhawan, B.; Gutsche, C. D. *J. Org. Chem.* **1983**, *48*, 1536; (c) For dihomoazacalixarenes, see: Khan, I. U.; Takemura, H.; Suenaga, M.; Shinmyozu, T.; Inazu, T. *J. Org. Chem.* **1993**, *58*, 3158.
7. Shudo, K.; Ohta, T.; Okamoto, T. *J. Am. Chem. Soc.* **1981**, *103*, 645.
8. For a discussion of the Bamberger rearrangement, see: Shine, H. J. In *Aromatic Rearrangements*; Eaborn, C.; Chapman, N. B., Eds.; Reaction Mechanisms in Organic Chemistry Monograph 6; Elsevier: New York, 1967, pp. 182–190.
9. Hudlický, M. In *Reductions in Organic Chemistry*; ACS Monograph 188; American Chemical Society: Washington, DC, 1996, pp. 94.
10. For a theoretical discussion on C-/N-substitution, see: Moran, R. J.; Cramer, C.; Falvey, D. E. *J. Org. Chem.* **1997**, *62*, 2742.
11. Boyle, A. *Theochem* **1999**, *469*, 15.

† General experimental procedure: To a stirred solution of 4-*tert*-butyl-2-nitroanisole (0.210 g, 1.0 mmol) in THF (30 mL) at 0°C was added 5% Pd/C (0.8 g) and hydrazine (0.8 mL). After stirring 2 h the solution was filtered, dried and evaporated to a yellow oil. The crude oil was dissolved in CH_2Cl_2 (10 mL) and *p*-*tert*-butylphenol (0.750 g, 5.0 mmol) was added followed by trifluoroacetic acid (0.2 mL, 2.5 mmol) and the solution was stirred overnight. The solution was then diluted with ether, transferred to a separatory funnel and washed sequentially with 5% HCl, water, saturated aqueous $NaHCO_3$, saturated aqueous NaCl, dried and evaporated. Excess *p*-*tert*-butylphenol was removed by sublimation and column chromatography (5% EtOAc/hexane) on the residual oil afforded diphenylamine **6** (0.197 g, 60%) as a tan oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, 2H, J=8.9 Hz), 6.84 (d, 2H, J=8.9 Hz), 6.77 (s, 1H), 6.40 (s, 1H), 3.69 (s, 3H), 3.1 (br s, 2H), 1.32, (s, 9H), 1.31 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5, 146.5, 145.9, 144.2, 133.9, 131.4, 126.2, 116.5, 113.7, 105.3, 55.7, 34.1, 34.0, 31.5, 30.5; IR (neat) 3464, 3376, 1603, 1503, 1223, 1073, 877, 831 cm^{-1}; HRMS $C_{21}H_{29}NO_2$ (FAB) calcd 327.2198, found 327.2191.

‡ Data for compound **7**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.91 (s, 1H), 7.30 (d, 2H, J=8.7 Hz), 6.78 (d, 2H, J=8.7 Hz), 6.61 (s, 1H), 6.15 (s, 1H), 4.29 (s, 2H), 1.24 (s, 9H), 1.23 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.4, 144.9, 143.9, 142.7, 131.9, 131.2, 126.4, 116.7, 113.0, 108.0, 34.0, 33.7, 31.4, 30.6; IR (neat) 3373, 3311, 1602, 1502, 1226, 876, 834 cm^{-1}; HRMS $C_{20}H_{27}NO_2$ (FAB) calcd 313.2042, found 313.2046.