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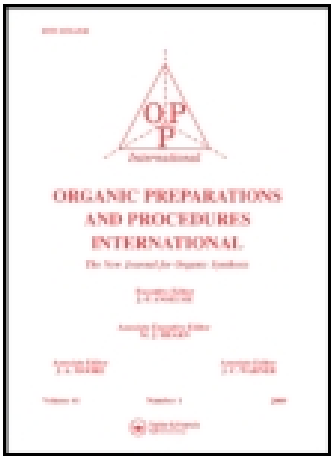

Organic Preparations and Procedures International: The New Journal for Organic Synthesis

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uopp20

A Concise Synthesis of (E)-3-Amino-1-phenyl-1-butene, a Monoamine Oxidase Inhibitor

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Published online: 10 Jul 2014.

To cite this article: Wellington Martins Ventura & Jason Guy Taylor (2014) A Concise Synthesis of (E)-3-Amino-1-phenyl-1-butene, a Monoamine Oxidase Inhibitor, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 46:4, 381-385, DOI: 10.1080/00304948.2014.922385

To link to this article: http://dx.doi.org/10.1080/00304948.2014.922385

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Organic Preparations and Procedures International, 46:381–385, 2014
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ISSN: 0030-4948 print / 1945-5453 online
DOI: 10.1080/00304948.2014.922385

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OPPI BRIEF

A Concise Synthesis of (*E*)-3-Amino-1-phenyl-1-butene, a Monoamine Oxidase Inhibitor

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The importance of allylic amines as useful building blocks for the synthesis of amino acids,[1–4] alkaloids,[5–7] and therapeutic agents[8, 9] has been well documented. The title compound is referred to as α-methylcinnamylamine in a report that describes its activity as a monoamine oxidase (MAO) inhibitor; MAO is an important target enzyme for the development of new drugs to treat MPTP-induced Parkinson's disease.[10] In spite of its importance as a useful building block for organic synthesis, it is not readily commercially available and is therefore usually prepared in the laboratory. Common synthetic methods include reductive amination of benzylideneacetone,[11,12] palladium-catalyzed substitution reaction of 4-phenyl-3-buten-2-yl acetate with sodium azide followed by reduction of the azide with triphenylphosphine,[13] or Grignard addition to cinnamonitrile.[14] Undoubtedly, the reductive amination of benzylideneacetone is the most attractive of the aforementioned protocols given the low cost of the reagent; however, stoichiometric quantities and even excess titanium(IV) isopropylate or zinc metal are usually required. These approaches generate large quantities of inorganic waste which renders them inconvenient for large scale syntheses. For this reason, we developed and now report a three-step strategy amenable to the gram-scale synthesis of (*E*)-3-amino-1-phenyl-1-butene which begins from inexpensive cinnamaldehyde and involves a hydroamination reaction catalyzed by a $Cu(OTf)_2$-2,2′-bipyridine complex in the key C-N bond forming step.

For the synthesis of 1-phenyl-1,3-butadiene, we adopted a known procedure[15] involving a Wittig reaction between *trans*-cinnamaldehyde and methyltriphenylphosphonium iodide in the presence of *t*-BuOK, but modified the solvent system and work up procedure to obtain the desired product as a transparent oil in 89% yield. The addition of carbamates to

Submitted by February 13, 2014.
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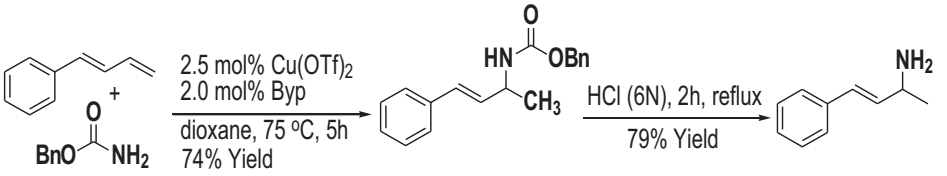
1,3-dienes had been reported to occur in the presence of a catalytic amount of $Cu(OTf)_2$ and diphosphine ligand.[16] Transitions metal salts with weakly coordinating anions generate Brønsted acids through cation hydrolysis. The active catalytic species is triflic acid which is generated *in situ* by trace amounts of water present in the solvent. The best yield was realized with 1,4-dioxane as solvent. For the present procedure, we employed 2,2′-bipyridine to regulate the active triflic acid concentration and avoid competitive polymerization of the diene which led to an improved yield of the hydroamination adduct. The addition of benzyl carbamate occurred exclusively at the terminal double bond with complete regioselectivity to yield *E*-4-phenyl-3-buten-2-amine *N*-benzyloxycarbonyl ester as a crystalline white solid. Finally, the free amine was liberated by straight forward deprotection of the carbamate group by acid catalyzed hydrolysis to afford the title compound in 58% yield in two steps (*Scheme 1*).



Scheme 1

The synthetic protocol for (*E*)-3-amino-1-phenyl-1-butene presented here was carried out on gram scale and was completed in only two days of laboratory work. The catalytic hydroamination reaction does not require an inert atmosphere or anhydrous solvents and $Cu(OTf)_2$ is more convenient and practical to manipulate than triflic acid. In a report describing the use of the $Cu(OTf)_2$-2,2′-bipyridine catalyst for the annulation of phenols with 1,3-dienes, the paramagnetic blue precipitate observed at the end of the reaction was recovered.[17] This polymeric copper(II) complex was reused in successive reactions, thus demonstrating the robustness and potential recyclability of the $Cu(OTf)_2$-2,2′-bipyridine complex for the hydroamination reaction. The characterization data for all compounds were in accordance with literature values cited.

Experimental Section

All reagents are commercially available and were used as received. Anhydrous solvents were purchased from Sigma Aldrich. Column chromatography was performed using silica gel 200–400 Mesh. TLC analyses were performed using silica gel plates, with ultraviolet light (254 nm) or vanillin solution used for visualization. Melting points were determined on a Buchi B-540 apparatus and are uncorrected. IR spectra were recorded on a Bomem FTIR MB- series B-100 model as either a liquid film between NaCl plates or as KBr pellets. NMR spectra were acquired on a Bruker 400 MHz spectrometer in $CDCl_3$. The chemical shifts are reported in δ referenced to residual solvent hydrogen. The coupling constant values (J) are expressed in Hertz (Hz).

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Synthesis of 1-Phenyl-1,3-butadiene

A suspension of methyltriphenylphosphonium iodide (20.0 g, 49.5 mmol) and potassium *tert*-butoxide (8.3 g, 74.1 mmol) in anhydrous THF (120 ml) was stirred for 10 min at 0°C under a nitrogen atmosphere. The reaction mixture was then treated with *trans*-cinnamaldehyde (6.3 ml, 50.0 mmol) and stirred for 5 h under reflux. Upon completion, the mixture was diluted with hexanes (50 ml) and the solid phosphine oxide was removed by filtration. The solvent was reduced under vacuum and the product was extracted from the gummy residue with *n*-hexanes (3 × 40 ml). Evaporation of the solvents under reduced pressure gave an oily residue which was purified by column chromatography to afford 1-phenyl-1,3-butadiene (6.4 g, 89%) as a transparent oil.; $R_f = 0.7$ (hexanes); IR (cm^{-1}): 3059, 3027, 1946, 1803, 1679, 1633, 1602; ^1H NMR (400 MHz) : δ 7.38 (2H, d, $J = 7.6$), 7.30 (2H, t, $J = 7.6$), 7.21 (1H, t, $J = 7.6$), 6.80 (1H, dd, $J =$ 10.8, 15.6), 6.55 (2H, m), 5.32 (1H, d, $J = 17.2$), 5.15 (1H, d, $J = 10.0$); ^{13}C NMR (100 MHz): δ 137.2, 137.1, 132.9, 129.6, 128.6, 127.6, 126.5, 117.7; *m/z* (EI): 130 (M^+, 100%), 111 (25%), 95 (20%), 67 (30%). The NMR data are in accordance with literature values.[18]

Synthesis of* E-*4-Phenyl-3-buten-2-amine N-Benzyloxycarbonyl Ester

In a round bottom flask (250 ml) equipped with a magnetic stir bar and reflux condenser were placed copper trifluoromethanesulfonate (297 mg, 0.85 mmol), 2,2′-bipyridine (102 mg, 0.67 mmol) and 1,4-dioxane (60 ml). Benzyl carbamate (5.0 g, 33 mmol) and 1-phenyl-1,3-butadiene (5.2 g, 40 mmol) were added to the flask and the mixture was stirred at 75°C for 5 h. Upon completion, the reaction mixture was diluted with ethyl acetate (40 ml) and washed with 1M aq. $NaHCO_3$ (40 ml). The layers were separated and the organic layer was dried over Na_2SO_4, concentrated under vacuum, and purified by column chromatography (3:1 hexanes/EtOAc) to provide the product as a crystalline white solid (6.9 g, 74%), mp. 82–84°C (lit.[19] 89–90°C); $R_f = 0.3$ (hexanes/EtOAc, 4:1); IR (cm^{-1}): 3320, 3026, 2982, 2939, 2898, 1950, 1876, 1681; 1H NMR (400 MHz): δ 7.39–7.28 (10H, m), 6.56 (1H, d, $J = 16.0$), 6.22 (1H, dd, $J = 6.0, 16.0$), 5.15 (2H, s) 4.84 (1H, br s), 4.51–4.55 (1H, br m), 1.38 (3H, d, $J = 6.8$); ^{13}C NMR (100 MHz): δ 155.6, 136.7, 136.6, 131.2, 129.6, 128.6, 128.2, 127.7, 127.6, 126.5, 126.4, 66.8, 48.5, 21.1; *m/z* (EI): 281 (M^+, 10%), 222 (30%), 190 (50%), 129 (60%), 91 (100%), 65 (15%), 42 (12%). The NMR data are in accordance with literature values.[20]

Synthesis of (E)- 3-Amino-1-phenyl-1-butene

In a round bottom flask (250 ml) equipped with magnetic stir bar and reflux condenser the protected amine (5.0 g, 17.8 mmol) was heated to reflux in 6N HCl (85 ml) with stirring for 1 h. The cooled solution was then taken up in to a separatory funnel and washed with dichloromethane (20 ml). The organic extract was discarded and the aqueous phase was basified with an aqueous solution of NaOH (10%) to pH 10–12. The free amine was extracted with dichloromethane (3 × 40 ml) and the combined organic extracts, dried and concentrated under vacuum on a rotary evaporator. The oily residue was purified by column chromatography (8:1:1 hexanes/EtOAc/Et_3N) to provide the

product as a pale yellow oil (2.1 g, 79%). IR (cm^{-1}): 3267, 3027, 2969, 1587,; ^{1}H NMP (400 MHz): δ 7.39–7.20 (5H, m), 6.45 (1H, d, $J = 16.0$), 6.20 (1H, dd, $J = 6.6$, 16.0), 3.70–3.62 (1H, m, 1H), 1.27 (3H, d, $J = 6.5$); ^{13}H NMP (100 MHz): 137.3, 136.1, 128.7, 127.6, 127.2, 126.4, 49.1, 23.9. The NMR data are in accordance with literature values.[21]

Acknowledgements

This work was supported by the Brazilian Funding Agency Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG) under research grant project codes APQ-00307-12, APQ-00356-13 and the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) under research grant project code 473461/2013-7. The authors gratefully acknowledge the generous financial support from the Universidade Federal de Ouro Preto and the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) for graduate research studentships and bursaries.

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