β-Phenylethylamines, Indolines and Isoquinolones via Hydroamination of Styrenes by Microwave Irradiation

Julio A. Seijas,* M. Pilar Vázquez-Tato,* M. Montserrat Martínez

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Santiago de Compostela, Aptdo. 280, 27080-Lugo, Spain
Fax +34 982 224904; E-mail: qoseijas@lugo.usc.es or pilarvt@lugo.usc.es

Received 12 February 2001

Abstract: Microwave irradiation promotes hydroamination of styrenes. This method can be used as a direct way of producing different kinds of bioactive compounds: open chain compounds like ß-phenylethylamines or cyclized products like indolines or isoquinolones.

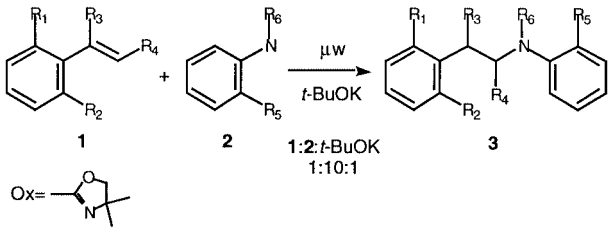
Key words: amination, domino reaction, indoline, isoquinolone, microwave heating, nucleophilic addition, phenethylamine

Synthesis of β-phenylethylamines has been always an object of interest due to their pharmacological properties, these compounds cover a wide range of different activities: antihistaminic, adrenergic, sympathomimethic, anorexic, etc.[1] Besides, the β-phenylethylamine fragment is a useful building block for many syntheses of more elaborated skeletons. Many natural products contain β-phenylethylamine in their skeleton either as an ethylamino branch or forming part of the polycyclic topologies -as is in the case of isoquinolinic and indole alkaloids.[2]

Our group has been focusing its interest on the reactivity of styrene derivatives with nucleophiles.[3] We have found that primary and secondary lithium amides added to styrene give β-phenylethylamines at 0 °C.[3c] From these studies we found out that when styrene was treated with lithium salt of aniline, under the same conditions for 24 h, no reaction was observed. Previously it had been reported[4] that when hydroamination of styrenes was carried out in a sealed tube at high temperatures, the addition reaction took place although in a wide range of yields. This, combined to our last report[5] on the synthesis of 4-aminoquinazolines by microwave irradiation of potassium salt of anthranilonitrile and different nitriles under microwave irradiation, led us to believe that microwaves could be used to promote the addition of aniline to styrene, avoiding the use of heating in sealed tubes and the need for solvent.

So, an equimolecular ratio of styrene and aniline were irradiated with a 10% potassium *tert*-butoxide yielding a 59% of *N*-phenyl-2-phenylethylamine. We optimized the reaction by checking the reagents ratio and we found that better yields were obtained for 1:10:1 ratio of styrene, aniline and potassium *tert*-butoxide respectively, which afforded *N*-phenyl-2-phenylethylamine in a yield of 81% (Scheme 1 and Table, entry 1). We affirmed the necessity of having an excess of aniline with respect to styrene and it is also important to keep the ratio of the base at 10% regarding aniline.

The scope of application of this microwave enhancement of hydroamination of styrene with base catalysis was determined by checking the influence of substitution either on the aniline or in the styrene. Thus, 2-methylaniline reacts with styrene affording *N*-(2-methylphenyl)-2-phenylethylamine in a 56% yield (Table, entry 2), despite the steric hindrance from the substituent in the *ortho* position. This product posseses the carbon skeleton of enfenamic acid, an antiinflamatory agent. However, when we heated anthranilic acid and styrene in the presence of potassium tert-butoxide, no addition product was isolated; only aniline from decarboxylated anthranilic acid was recovered. This enhancing of the decarboxylation of aromatic acids by microwaves was recently reported,[6] but only in the presence of quinoline/Cu(II) or *N*-ethylmorpholine. As a masking group to avoid decarboxylation we used nitrile. Thus, anthranilonitrile was irradiated with microwaves together with styrene and potassium *tert*-butoxide, but no addition product was obtained, only 4-amino-2-(2-aminophenyl)quinazoline from self condensation was formed. One reason to explain the lack of addition between styrene and anthranilonitrile can be found in their frontier orbitals.[7]



Scheme 1 Hydroamination of styrenes to β-phenylethylamines.

We also explored the influence of the presence of a second nitrogen atom in the nucleophilic center; thus, phenylhydrazine gave a 85% yield of 1-(2-phenylethyl)-1-phenylhydrazine (Table, entry 3).

Substituted styrenes in the double bond like β-methylstyrene and α-methylstyrene, in the same conditions yielded *N*-phenyl-1-methyl-2-phenylethylamine and *N*-phenyl-2-methyl-2-phenylethylamine respectively, but in moderate yields (Table, entries 4 and 5).

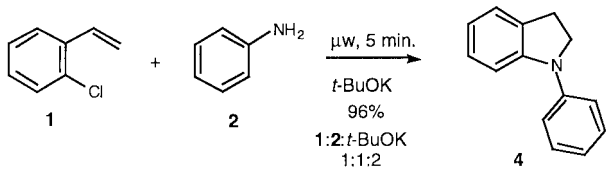
We also studied the behavior of 2-chlorostyrene, since as shown by Beller et al.,[4b] this compound presents the possibility of suffering a domino reaction giving an indoline

Table Hydroamination of styrenes to β-phenylethylamines

Entry	Styrene (1)				Amine (2)		Time	Yield 3[a]
	R_1	R_2	R_3	R_4	R_5	R_6	(min)	(%)
1	H	H	H	H	H	H	10	81
2	H	H	H	H	Me	H	10	56
3	H	H	H	H	H	NH_2	1.5	85
4	H	H	H	Me	H	H	10	44
5	H	H	Me	H	H	H	10	42
6	Cl	H	H	H	H	H	3	67
7	OMe	Ox	H	H	H	H	5	100

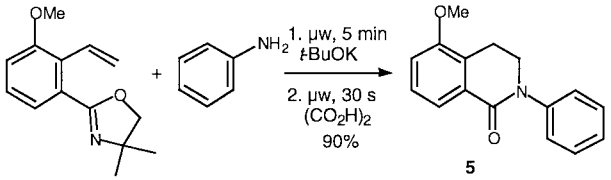
[a]These reactions were carried out with a reagents ratio of styrene:aniline:*t*-BuOK, 1:10:1.

structure. This fragment is present in a large number of products with biological and pharmacological interest for instance analgesics.[8] We have found that the structure of the final product could be controlled by the reaction conditions, if we use a ratio of styrene:aniline:*t*-BuOK 1:10:1. *N*-Phenyl-2-(2-chlorophenyl)ethylamine was the reaction product in a 67% yield after 3 minutes of irradiation, originating from the addition of aniline to the styrenic double bond (Table, entry 6), with no cyclization product. However, if the ratio of reagents was 1:1:2 the addition-cyclization product **4** was achieved in a very good yield (96%), after 5 min of irradiation (Scheme 2). This microwave enhanced cyclization to indoline gave a yield almost twice as high, and four hundred times faster, than the yields previously reported with conventional heating, without the appearance of the oxidation subproduct previously described for this reaction.



Scheme 2 Domino hydroamination-cyclization of styrene to give N-phenylindoline.

This methodology can be used to prepare another interesting ring system: the isoquinolinic one, which is present in a great number of natural products of biological significance.[2] We envisaged 2-(2-carboxyphenyl)ethylamines as precursors to *N*-phenyl-3,4-dihydroisoquinolin-1-ones; thus we heated 2-carboxystyrene with aniline and base, but only decomposition products were obtained, even with very short irradiation times. We turned our attention to oxazoline ring as protection for the acid group; so we reacted 2-(3-methoxy-2-vinylphenyl)-4,4-dimethyl-2-oxazoline[9] with aniline and we obtained the corresponding β-phenylethylamine **3** (Table, entry 7) in a quantitative yield. This excellent yield confirmed our previous studies on the behavior of these compounds towards 1,6-conjugated additions of nucleophiles.[3] Afterwards this compound, without any further purification, was irradiated under microwaves for 30 seconds, with oxalic acid yielding **5** in 90%, and provided a good one-pot cyclization procedure for this ring system (Scheme 3). To our knowledge this is the first time microwave mediated hydrolisis of oxazoline group is reported.



Scheme 3 One pot hydroamination-cyclization of *o*-vinylphenyloxazolines to afford *N*-phenyl-3,4-dihydroisoquinolin-1-ones.

In summary, here we present a method based on the hydroamination of styrenes by irradiation in a domestic microwave oven in the presence of potassium *tert*-butoxide. It proved to be an efficient method in the preparation of three different skeletons of great importance in the chemistry of biologically active products.[10] By choosing adequate precursors lineal compounds (β-phenylethylamines), five-membered cyclization products (indolines) or six-membered cyclization products (isoquinolones) can be obtained, all in one pot reaction. The good to excellent yields, together with the green chemistry aspect of microwave heating without a solvent, and the easiness of preparation (avoiding the use of pressure vessels), make this procedure a useful tool for organic synthesis.

Acknowledgement

The authors thank DGES for financial support (PB96-0932).

References and Notes

(1) a) *The Merck Index*, 12th ed.; Budavari, S., Ed.; Merck& Co., Inc.: Whitehouse Station, NJ **1996**. b) Shulgin, A.; Shulgin, A. *PiHKAL: A Chemical Love Story*; 2nd half. Transform Press. Berkeley.
(2) *Comprehensive Natural Products Chemistry*, Barton, D.; Nakanishi, K., Eds.; Elsevier: Amsterdam, 1999.
(3) a) Seijas, J. A.; Vázquez-Tato, M. P.; Castedo, L.; Estévez, R. J.; Ruíz, M. *J. Org. Chem.* **1992**, *57*, 5283-5284. b) Martínez, M. M.; Ónega, M. G.; Tellado, M. F.; Seijas, J. A.; Vázquez-Tato, M. P. *Tetrahedron* **1997**, *41*, 14127-14130. c) Seijas, J. A.; Vázquez-Tato, M. P.; Entenza, C.; Martínez, M. M.; Ónega, M. G.; Veiga, S. *Tetrahedron Lett.* **1998**, *39*, 5073-5076.
(4) a) Wegler, R.; Pieper, G. *Chem. Ber.* **1950**, *83*, 1. b) Beller, M.; Briendl, C.; Riermeier, T. H.; Eichberger, M.; Trauthwein, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 3389. c) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675-703.

(5) Seijas, J. A.; Vázquez-Tato, M. P.; Martínez, M. M. *Tetrahedron Lett.* **2000**, *41*, 2215-2217.
(6) Frederiksen; L. B.; Grobosch, T. H.; Jones; J. R.; Lu, S.-Y.; Ahao, C.-C. *J. Chem. Res., Synop.* **2000**, 42-43.
(7) The energy gap between the HOMO of the potassium salt of anthranilonitrile and the LUMO of styrene is wider than the gap between the HOMO of the salt of anthranilonitrile and the LUMO of anthranilonitrile. Meanwhile benzonitrile has a lower lying LUMO than anthranilonitrile, and in this case the 4-aminequinazoline from anthranilonitrile and benzonitrile is obtained instead of the 4-aminoquinazoline from self-condensation of anthranilonitrile.[5] PCGAMESS and MacMolPlt, with 3-21G** basis for *ab initio* calculations in the gas phase were used.
(8) a) Glamkowski, E. J.; Fortunato, J. M. U.S. Patent 4 448 784, 1984; *Chem. Abstr.* **1985**, *101*, 151748e.
(9) Meyers, A. I.; Gabel, R.; Mielich, E. D. *J. Org. Chem.* **1978**, *43*, 1372-1379.
(10) General Procedure. *N*-Phenyl-2-phenylethylamine (**3**): A mixture of styrene (100 mg, 0.962 mmol), aniline (895 mg, 9.62 mmol) and potassium *tert*-butoxide (107 mg, 0.962 mmol) in a open test tube was heated in a domestic microwave (1000 W, 70% of total power) until no starting styrene was observed by TLC (10 min.). The crude reaction was purified by chromatography column on silicagel to afford *N*-phenyl-2-phenylethylamine (154 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43-7.26 (m, 7H), 6.82 (t, 1H, J = 7.2 Hz), 6. 72 (d, 2H, J = 7.6 Hz), 3.87 (br s, 1H), 3.48 (t, 2H, J = 7.0 Hz), 3.0 (t, 2H, J = 7.0 Hz). IR (KBr, film): 3415 (NH) cm^{-1}. *N*-Phenyl-2,3-dihydroindole (**4**): The procedure was similar as for **3,** reacting *o*-chlorostyrene (100 mg, 0.721 mmol), aniline (67 mg, 0.721 mmol) and potassium *tert*-butoxide (162 mg, 1.442 mmol) during 5 min., yielding *N*-phenyl-2,3-dihydroindole (**4**)[4b] (135 mg, 96%). 5-Methoxy-*N*-phenyl-3,4-dihydroisoquinolin-1-one (**5**): A mixture of 2-(3-methoxy-2-vinylphenyl)-4,4-dimethyl-2-oxazoline (122 mg, 0.528 mmol), aniline (492 mg, 5.28 mmol) and *tert*-butoxide potassium (59 mg, 0.528 mmol) was heated as the procedure stated above during 5 min. To the crude mixture was added oxalic acid (600 mg, 6.67 mmol) and irradiated during 30 seconds. Reaction mixture was dissolved in CH_2Cl_2 and washed with aq. NaOH 10%, aq. HCl 10% and water. The organic layer was dried (Na_2SO_4), and evaporated to give chomatographically pure 5-methoxy-*N*-phenyl-3,4-dihydroisoquinolin-1-one (**5**) (120 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.79 (d, 1H, J = 8.0 Hz), 7.42-7.20 (m, 6H), 7.03 (d, 1H, J = 8.5 Hz), 3.97 (t, 2H, J = 6.5 Hz), 3.90 (s, 3H), 3.12 (t, 2H, J = 6.5 Hz). IR (KBr): 1670 (CON) cm^{-1}. M. p. 246-248 (Cl_2CH_2).

Article Identifier:
1437-2096,E;2001,0,06,0875,0877,ftx,en;D03701ST.pdf