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A novel method for the efficient synthesis of 2-arylamino-2-imidazolines

Sreenivasa R. Mundla,[a,*] Larry J. Wilson,[b] Sean R. Klopfenstein,[b] William L. Seibel[b] and Nick N. Nikolaides[b]

[a]*Procter & Gamble Pharmaceuticals, Chemical Development, Woods Corners, PO Box 191, Norwich, NY 13815, USA*

[b]*Procter & Gamble Pharmaceuticals, Health Care Research Center, 8700 Mason-Montgomery Road, Mason, OH 45040, USA*

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Abstract

A novel method for the efficient synthesis of 2-arylamino-2-imidazolines is described.

Keywords: aminoimidazoline; 2-methythio-2-imidazoline; arylamine; benzimidazole.

Aminoimidazoline derivatives **1** have been used broadly in medicine, as cardiovascular antihypertension agents, as sedatives and analgesics, as agents for the treatment of drug and alcohol withdrawal symptoms, as diuretic agents, as antidiarreheal agents, and as agents which lower intraocular pressure.[1] For example, clonidine is one of the most widely known alpha-2-adrenoreceptor agonists and antihypertensive agents.[2a] Indanazoline is a useful vasoconstrictive agent.[2b,c] Over the past four decades, a number of methods to produce these aminoimidazoline derivatives **1** from the corresponding arylamines **2** have been reported in the literature. For example, Chapleo et al.[3] have reported the synthesis of clonidine analogs by reacting an aromatic amine with 2-methylthio-2-imidazoline in the presence of pyridine. One of the most commonly used approaches entails a three-step protocol involving the conversion of an amine to the isothiocyanate, treatment of the isothiocyanate with ethylenediamine, followed by a cyclization step using mercuric oxide or acetate to form the 2-amino-2-imidazoline.[4] Recently, Munk et al.[5] have reported that yields in the formation of 2-amino-2-imidazolines can be moderately improved over Chapleo's procedure by coupling an aromatic primary amine with an imidazoline sulfonic acid. There had also been reports in which a 2-chloro-2-imidazoline is coupled with an amine.[6] From our experience, many of the known methods have one or more limitations. For example,

* Corresponding author. Present address: P&G Pharmaceuticals, Health Care Research Center, 8700 Mason-Montgomery Rd, Mason, OH 45040, USA. Tel: 001-513-622-2327; fax: 001-513-622-2675; e-mail: mundlasr@pg.com

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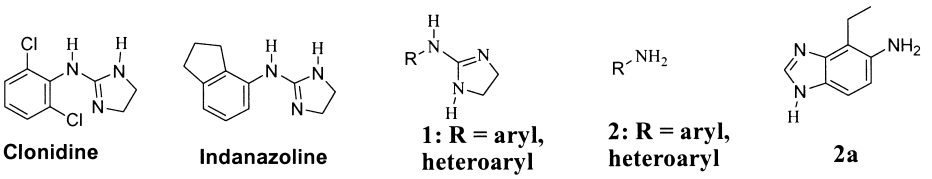
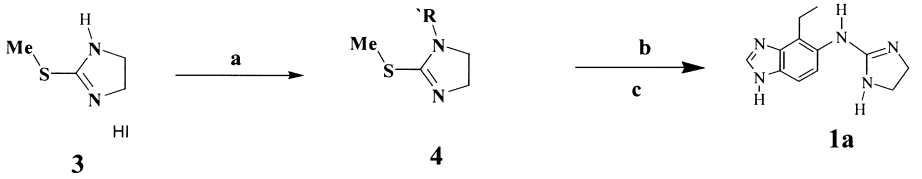
using toxic reagents like mercuric acetate, low yields, aqueous work-up procedures during isolation and harsh reaction conditions. Thus, we decided to develop a more economical and high yielding method suitable for producing a wide variety of aminoimidazoline derivatives.



In this communication, we wish to disclose a highly efficient, convergent method for the synthesis of 2-arylamino-2-imidazolines **1** from the corresponding arylamines **2**. As shown in Scheme 1, this method involves the preparation of an *N*-acylated-2-methylthio-2-imidazoline derivative **4** and its coupling with an arylamine **2** in a protic solvent followed by removal of the protecting group in the same pot under relatively mild conditions.



Scheme 1. Reagents and conditions: (a) acylating agent, $(CH_2Cl)_2$ or DMAC, TEA, 0°C to rt, 2–6 h; (b) **2a**, 10% AcOH/EtOH, rt to 65°C, 16 h; (c) reflux, 14 h

As shown in Scheme 1 and Table 1, we conveniently synthesized a variety of *N*-acylated-2-methylthio-2-imidazoline derivatives **4a**–**g** from the commercially available 2-methylthio-2-imidazoline hydroiodide **3**, which can also be prepared by reaction of ethylenethiourea with iodomethane.[7a] Thus, exposure of **3** to an acylating agent (see Table 1) in the presence of triethylamine furnished **4** in excellent yields.[7b,10] This method of preparation of **4b** and **4e** is more convenient and is higher yielding than the method reported by Kohn et al.[8a,b] They have reported the preparation of **4b** from ethylenethiourea, first by converting into an *N*-carbomethoxyimidazolidinethione in 32% yield, followed by alkylation with iodomethane and chromatographic purification in 61% yield. Similarly, they have prepared **4e** by alkylating the *N*-acetylimidazolinethione[9] with iodomethane in 38% yield.

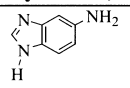
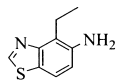
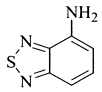
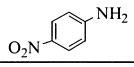
Table 1

Entry	Acylating agent	4	Yield of 4	Yield of 1a
a	$(Me_3COOC)_2O$	R = $COOCMe_3$	97%	85%
b	ClCOOMe	R = COOMe	96%	90%
c	ClCOOallyl	R = COOallyl	98%	90%
d	ClCOOPh	R = COOPh	92%	88%
e	$(CH_3CO)_2O$	R = COMe	94%	90%
f	$(CH_3CH_2CO)_2O$	R = COEt	97%	88%
g	PhCOCl	R = COPh	90%	96%

As summarized in Table 1, individual reaction of the 4-ethyl-5-aminobenzimidazole **2a** with various imidazoline precursors **4a**–**g** in 10% acetic acid–ethanol (15 ml/g) at 60–75°C for 10–16 h, followed by heating to reflux for 14 h, furnished the 2-arylamino-2-imidazoline derivative **1a** in good yield.[10] The product **1a** was isolated as a di-acetate salt. The isolation process involves concentration of the reaction mixture to an oily residue followed by crystallization. This method of isolation avoided the laborious aqueous work-up.

When we applied this convergent method to produce a variety of substituted 2-arylamino-2-imidazolines, we found that the reaction conditions described above worked well with electron-rich arylamines. Arylamines in which the amino group is either sterically hindered (2,6-dichloroaniline) or which bear an electron withdrawing group (4-nitroaniline) did not perform as well. As shown in Table 2, by using modified reaction conditions, we have successfully applied this method to the synthesis of a representative set of 2-arylamino-2-imidazolines **1** and isolated them as the acetate salts.[10]

Table 2

Entry	4	Arylamine, 2	Coupling Reaction Conditions	Yield of 1
i	R = $COOCMe_3$		a. 10% Acetic acid/EtOH, 60-65°C, 16h. b. Reflux, 6h	85%
ii	R = COOMe		a. 10% Acetic acid/MeOH, 60-65°C, 16h. b. Reflux, 6h	90%
iii	R = $COOCMe_3$		a. 10% Acetic acid/2-propanol 90°C, 19h	83%
iv	R = COOMe		a. Acetic acid, 65-75°C, 16h b. 75% MeOH/water, reflux, 16h	85%
v	R = COOMe		a. Acetic acid, 65-75°C, 16h b. 75% MeOH/water, reflux, 16h	80%

In summary, we have developed an efficient method for the convergent synthesis of a variety of 2-arylamino-2-imidazoline derivatives **1** from the corresponding aryl amines **2**. This method was found to be highly advantageous over the other known methods and suitable for large scale preparations, as it is high yielding, and avoids the use of toxic reagents and harsh reaction conditions. In addition, the procedure for the synthesis of *N*-protected 2-thiomethyl-2-imidazolines is very simple and also high yielding.

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7. (a) Aspinall, S. R.; Bianco, E. J. *J. Am. Chem. Soc.* **1951**, *73*, 602. (b) Synthesis of **4b**: To a stirred suspension of 2-methylthio-2-imidazoline hydroiodide (**3**; 4.5 g, 18.4 mmol) in dichloroethane (15 ml) was added triethylamine (1.4 ml). The resulting homogeneous solution was cooled in an ice bath at 0–5°C and methyl chloroformate (2.36 g, 25 mmol) was added in a dropwise manner. After completion of addition, the reaction mixture was allowed to warm up to room temperature and stirred for 6 h. The reaction mixture was concentrated under reduced pressure. Ethyl acetate (150 ml) was added to the residue and the mixture was filtered to remove the insoluble salts. The salts were rinsed with ethyl acetate (25 ml) and the combined filtrates were concentrated under reduced pressure to furnish **4b** (3.07 g, 96%).
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10. All products were identified by proton NMR and MS spectral data.