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Semmler–Wolff aromatisation: a concise route for the synthesis of 5-amino-quinazolines and 4-amino-indoles

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ABSTRACT

A simple and efficient methodology for the synthesis of 5-amino-quinazolines and 4-amino-indoles via Semmler–Wolff aromatisation reaction has been carried out. The oximation of keto intermediates followed by Semmler–Wolff aromatisation using acetic anhydride and a catalytic amount of sodium iodide in xylene provided the desired quinazolines and indoles.

The aromatisation of α,β-unsaturated cyclohexenyl ketoximes into corresponding aromatic amines under acidic conditions was first discovered by Semmler[1] and further explored by Wolff.[2] In the acidic medium, the reaction competes with Beckmann rearrangement and ketooxime prefers to aromatise to yield desired arylamine.[3] The reaction has been well studied with various cyclic and bicyclic oximes to generate corresponding carbocyclic and heterocyclic molecules.[4] The advantage of this reaction is that it places the amine functionality at a specific position of the aryl system in a simple manner which otherwise is difficult to introduce or synthesise by any other routes. One can visualise the application of Semmler–Wolff aromatisation reaction for the synthesis of pharmaceutically important heterocyclic compounds given in Figure 1 through appropriate oximes. The medicinal and biological value of these compounds has stimulated an extensive research in the area for their synthesis as they possess a wide spectrum of pharmaceutical and biological properties including anti-inflammatory (a, b),[5] dengue virus inhibitor (c),[6] antiphlogistics[7] and antibacterial (Fig. 1).[8]

During our search for a safe process for 4-acylaminoindole,[9] we applied Semmler–Wolff aromatisation reaction to its synthesis utilising the strategy as described in Scheme 1. This led us to the development of a safe manufacturing process for AZD1981.[9] Employing the same strategy, we further visualised the application of Semmler–Wolff aromatisation to the synthesis of indazole and recently reported the synthesis of a series of indazoles using this approach (Scheme 1).[10]

This Letter describes yet another application of Semmler–Wolff aromatisation to the synthesis of 5-amino-quinazolines and 4-amino-indoles. (Scheme 2)

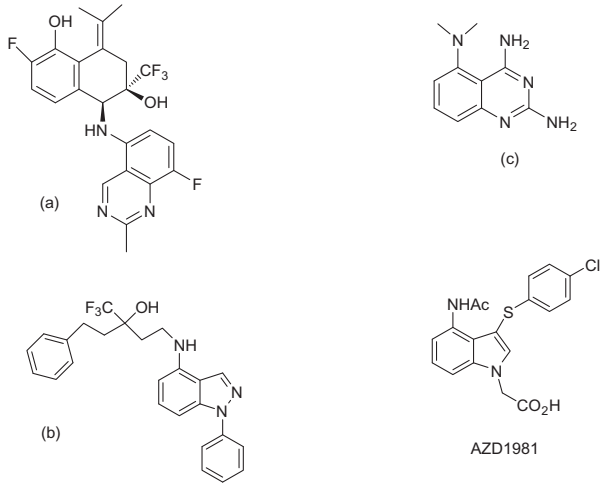

Figure 1. Biologically and pharmacologically active amino substituted compounds.

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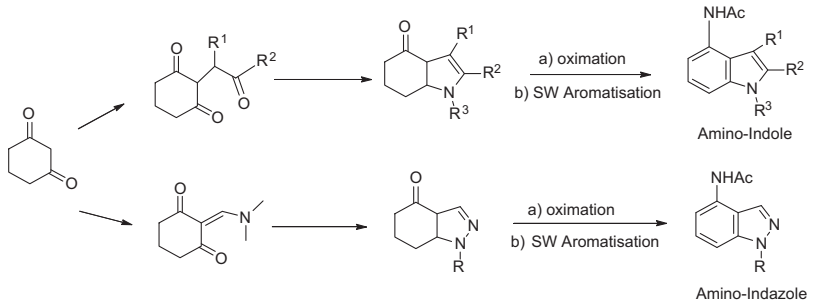
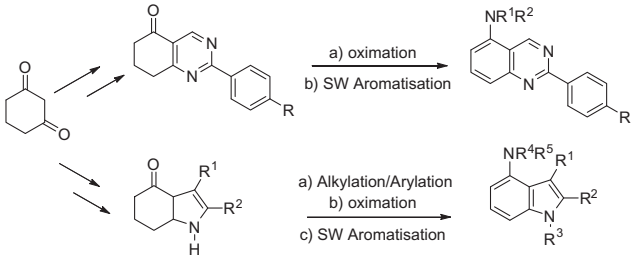
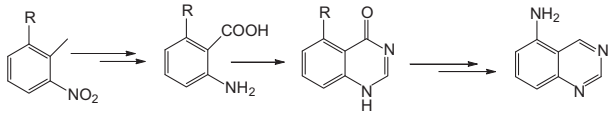


Scheme 1.



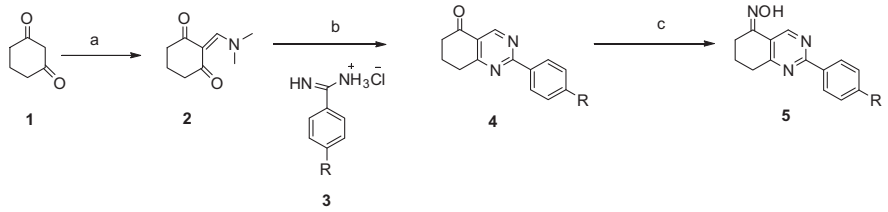
Scheme 2.



Scheme 3. Synthesis of 5-aminoquinazoline.

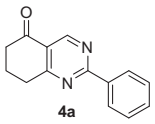
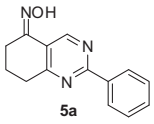
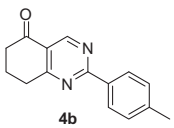
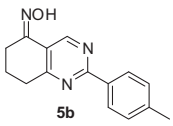
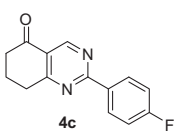
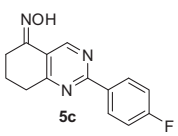
Various reports have been published for the synthesis of quinazolines and indoles which involves multiple synthetic steps. Synthesis of quinazolines have been reported from *N*-phenyl dimethyl propanamide,[7] substituted benzyl amine[11] and benzonitrile.[12] However, very few methods are known for the synthesis of 5-aminoquinazolines. The current known method involves the of 3-substituted anthranilic acid with amidines and further to 5-aminoquinazolines as shown in Scheme 3.[13–16] The major drawback in this synthesis is the availability of appropriate 1,2, 3-trisubstituted nitro compounds and the safety issues involved in handling.

In the present Semmler–Wolff strategy for the synthesis of 5-aminoquinazolines, the required ketointermediates (**4**) were prepared by the reaction of enamide (**2**) with benzamidine hydrochloride (**3**) using the reported procedure.[17] Further **4** was reacted with hydroxyl amine to get the corresponding oximes (**5**) needed for exploring Semmler–Wolff aromatisation chemistry. (Scheme 4). For example, 2-phenyl-7, 8-dihydro-6*H*-quinazolin-5-one (**4a**) was obtained from 2-dimethylaminomethylene



Scheme 4. R=H, CH_3, fluoro, OCH_3, Br, NO_2. Reaction conditions: (a) *N*,*N*-dimethylformamide dimethylisopropyl acetal, toluene, reflux; (b) IPA, water, aq HCl (catalytic), 65–70 °C, 16 h; (c) $NH_2OH{\cdot}HCl$, NaOAc, water, IPA, 65–70 °C, 2 h.

Table 1
Derivatives of oximes

Entry	Substrate	Product	Reaction time (h)	Isolated/conversion yield (%)
1	 **4a**	 **5a**	2	84[a]
2	 **4b**	 **5b**	2	65[a]
3	 **4c**	 **5c**	2	80[a]