A novel one-pot synthesis of 2-arylquinolines through cascade reactions mediated by samarium reagents

Xuesen Fan and Yongmin Zhang

Department of Chemistry, Zhejiang University at Xixi Campus, 310028, Hangzhou, Zhejiang, China
State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 200032, Shanghai, China
Department of Chemistry, Henan Normal University, 453002, Xinxiang, Henan, China

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A novel one-pot synthesis of 2-arylquinolines 4 from o-nitrobenzaldehydes 1 and α-haloketones 2 through Sm(I) and Sm(II) mediated cascade reactions is reported. The advantages of this new one-pot procedure are easily accessible substrates, simple and mild reaction conditions.

Quinolines and their derivatives occur in numerous natural products. Many quinolines display interesting physiological activities and have found attractive applications as pharmaceuticals and agrochemicals as well as being general synthetic building blocks. Many synthetic methods have been developed for quinolines, but due to their great importance, the development of novel and convenient synthetic methods remains an active research area.

Since pioneering studies by Kagan and co-workers demonstrated the particular effectiveness of samarium diiodide as a mild, neutral, and versatile single electron transfer reductant, the utilization of SmI₂ in organic synthesis has been well-documented. In addition, the reports of using samarium(III) in organic chemistry have also increased rapidly in recent years. For example, we have reported that, promoted by SmI₂, α-haloketones can react with aldehydes to give α,β-unsaturated ketones and α-diketones or α-ketoesters can condense with aldehydes to form benzyldiene-substituted α-diketones or α-ketoesters in fair yields. It was also reported that SmI₂ can successfully promote inter- and intra-molecular reductive coupling of a cyano group with a carbonyl group or a cyano group with a nitro group.

These results prompted us to investigate the possibility of one-pot synthesis of 2-arylquinolines 4 from o-nitrobenzaldehydes 1 and α-haloketones 2 through cascade reactions promoted by SmI₂ and SmI₃ without isolating the intermediate, o-nitrochalcones 3 from the reaction mixture (Scheme I). The characterization data of 4 are given in Table I.

Results and Discussion

When o-nitrobenzaldehydes 1 and α-haloketones 2 were treated with 1 equiv. SmI₃ for about 4–5 hr at room temperature, almost all of them were consumed and the corresponding o-nitrochalcones 3 were formed. Then, 3 equiv. samarium powder was added to the flask and the colour of the reaction mixture changed from dark red into deep brown gradually, showing that Sm(III) has been reduced to Sm(II) by metal samarium. In the meantime, the samarium (II) generated in situ efficiently promoted the intramolecular reductive coupling of the nitro group with the carbonyl group in o-nitrochalcones 3 to give 2-arylquinolines 4 in moderate yields (Table I).

Mechanism

Although the detailed mechanism of the above reaction has not been clarified yet, it is proposed that 2-arylquinoline derivatives 4 may be formed through SmI₃ and SmI₂ mediated cascade reactions (Scheme I). In the first place, mediated by SmI₃, a samarium (III) enolate intermediate is formed from α-haloketone 2, which then undergoes aldol-like reaction with o-nitrobenzaldehyde 1 to give o-nitrochalcone 3. In the second step, by addition of metal samarium to the reaction mixture, Sm (II) is generated through
the reaction between Sm (0) and Sm (III). As one of the efficient reductive coupling reagents, Sm (II) can promote the intra-molecular reductive coupling reaction between nitro group and carbonyl group in o-nitroaldehyde 3 to afford 2-arylquinoline\(^4\).

In conclusion, we have provided a new route to 2-arylquinolines, the advantages of which include one-pot synthesis from accessible substrates, simple and mild reaction conditions. Further studies to develop other new uses of SmI\(_3\) and SmI\(_2\) promoted cascade reactions are in progress.

**Experimental Section**

Tetrahydrofuran (THF) was distilled from sodium-benzophenone immediately prior to use. All reactions were conducted under a nitrogen atmosphere. Melting points are uncorrected. IR spectra were recorded on a Bruker Vector 22 spectrometer in KBr with absorption in cm\(^{-1}\); \(^1\)H NMR spectra on a Bruker AC–80 spectrometer in CDCl\(_3\) using TMS as internal standard (chemical shifts in \(\delta\), ppm); and mass spectra on a HP 5989B MS spectrometer.
General procedure for preparation of 2-arylquinolines 4. Under an inert atmosphere of nitrogen, a mixture of powdered samarium (0.15 g, 1 mmole) and iodine (0.375 g, 1.5 mmole) in dry THF (20 mL) was stirred at room temperature until samarium disappeared. To the resulting pale yellow suspension of SmI₃, was added simultaneously an o-nitrobenzaldehyde 1 (1 mmole) and a α-haloketone 2 (1 mmole) and the mixture was stirred at room temperature until 1 and 2 were almost consumed (monitored by TLC). Then 3 equiv. samarium powder was added to the flask and the colour of the reaction mixture changed into deep brown gradually. After being stirred for 3 hr at 50°C, the solution was quenched with dil. HCl (0.1 mL, 5 mL) and extracted with ether (3 × 20 mL). The combined extracts were washed with a saturated solution of Na₂S₂O₃ (15 mL), saturated brine (15 mL) and dried over anhydrous Na₂SO₄. After evaporating the solvent under reduced pressure, the crude product was purified by preparative TLC on silica gel using ethyl acetate-cyclohexane (1:6) as eluent to afford 4 (see Table I).

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References