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SmI_2-mediated facile one-pot preparation of 2,4-diarylquinolines from 3-aryl-2,1-benzisoxazoles

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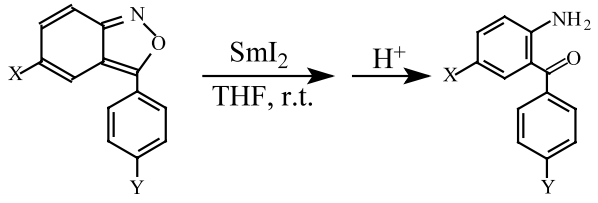
Abstract—On treatment with SmI_2, 3-aryl-2,1-benzisoxazoles undergo reductive cleavage of the N–O bond leading to 2-aminobenzophenones in high yields upon protonation. If aryl methyl ketones are added to the reaction mixture prior to protonation, the desired 2,4-diarylquinolines can be obtained in moderate yields under mild conditions.

The use of 2-aminobenzophenones as starting materials for the synthesis of a wide variety of heterocyclic systems is well documented.[1] Recently, it was also reported that 2-aminobenzophenones can be used as important intermediates in the preparation of numerous CNS drugs of the 1,4-benzodiazepine class.[2] As for quinolines and their derivatives, they occur in numerous natural products and display interesting physiological activities and have found attractive applications as pharmaceuticals and agrochemicals as well as being general synthetic building blocks.[3] Due to their great importance, many synthetic methods have been developed for 2-aminobenzophenones[4] and quinolines,[5] respectively. Moreover the development of more convenient and practical synthetic methods still remains an active research area.[6,7]

Kagan's reagent, samarium(II) iodide, is an exceptionally effective reagent for promoting reductive reactions, and the chemistry of this reagent has been well documented in several reviews.[8] The reactivity of SmI_2 towards various nitrogen-containing organic compounds[9] including nitro compounds, imines, oximes, hydrazones, azo and azide compounds has already been examined and it has also been reported that SmI_2 can promote the selective reduction of isoxazoles to give enamino ketones.[10] However, to our knowledge, there are no literature precedents for the reductive cleavage of the N–O bond in 3-aryl-2,1-benzisoxazoles by this reagent to give 2-aminobenzophenones upon protonation, or 2,4-diarylquinolines on treatment with aryl methyl ketones prior to protonation. Herein, we wish to report this novel process.

When 2,1-benzisoxazoles **1** were added to a solution of 2 equiv. of SmI_2 in THF at room temperature under a nitrogen atmosphere, the deep blue color of SmI_2 changed to a deep brown-red color immediately. TLC

Table 1. SmI_2-mediated conversion of 2,1-benzisoxazoles into 2-aminobenzophenones



1 **2**

Entry	X	Y	Reaction time (min)	Yield (%)[a]
1	Cl	H	5	90
2	Cl	Br	5	84
3	Cl	Cl	5	82
4	Cl	OCH_3	5	85
5	Br	H	5	86
6	Br	Cl	5	78

[a] Isolated yields based on 2,1-benzisoxazoles.

Keywords: samarium(II) iodide; 2-aminobenzophenones; quinolines; 2,1-benzisoxazoles; reductive cleavage.

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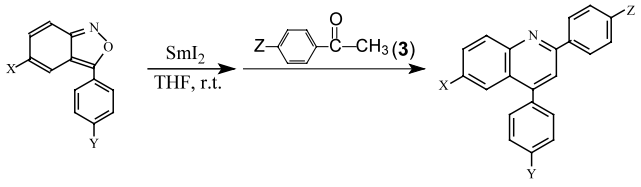
showed that the reductive cleavage of the N–O bond in 3-aryl-2,1-benzisoxazoles was complete within a few minutes and afforded 2-aminobenzophenones **2** smoothly upon subsequent protonation. The results are summarized in Table 1.

Several methods have already been reported for the preparation of 2-aminobenzophenones. The classical method for the preparation of 2-aminobenzophenones requires appropriately substituted anilines and high temperature reaction conditions;[11] catalytic reduction of 2,1-benzisoxazoles necessitates the use of expensive palladium.[12] In addition, aluminium triiodide has also been used to promote the cleavage of 2,1-benzisoxazoles to give 2-aminobenzophenones under reflux conditions.[6a] Compared with the methods mentioned above, our process has the advantages of milder reaction conditions, a shorter reaction time and a cheap reagent.

With the success of the preparation of 2-aminobenzophenones from 3-aryl-2,1-benzisoxazoles and bearing in mind that 2-aminobenzophenones have been used in the preparation of heterocyclic compounds by reacting with various carbonyl compounds, we then investigated the possibility of the one-pot preparation of 2,4-diarylquinolines directly from 3-aryl-2,1-benzisoxazoles and acetophenones. When acetophenone (0.6 mmol) was added to the deep brown-red colored reaction mixture resulting from treatment of 3-phenyl-5-chloro-2,1-benzisoxazole (0.5 mmol) with a solution of SmI_2 (1 mmol) in THF, the color of the reaction mixture faded gradually and eventually changed into a light-yellow color within an hour. Subsequent separation of the reaction mixture afforded 5-chloro-2,4-diphenylquinoline **4a** in moderate yield. Several other substrates bearing different functional groups have also been investigated and all gave 2,4-diarylquinoline derivatives in moderate to good yields (Table 2).

Table 2. SmI_2-mediated preparation of 2,4-diarylquinolines from 2,1-benzisoxazoles and aryl methyl ketones



1 **4**

Entry	X	Y	Z	Yield (%)[a]
a	Cl	H	H	62
b	Cl	H	CH_3	70
c	Cl	H	Cl	72
d	Cl	H	Br	70
e	Cl	Cl	Br	62
f	Cl	OCH_3	H	65
g	Cl	OCH_3	CH_3	68
h	Cl	OCH_3	Cl	66
i	Cl	OCH_3	Br	56
j	Cl	Br	Br	52

[a] Isolated yields based on 2,1-benzisoxazoles.

There have been reports on the preparation of 2,4-disubstituted quinolines in the literature. For example, the construction of quinoline derivatives has been accomplished through the reaction between *N*-arylideneanilines and alkynes in the presence of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ)[13] or di-isopropyl peroxydicarbonate (DPDC).[14] 2,4-Disubstituted quinolines can also be prepared through the condensation of 2-aminobenzophenone with ketones, but this process requires harsh conditions such as an acid or base as catalyst and moderate to high thermal conditions.[1b] In our hands, 2,4-diarylquinolines can be obtained directly from 3-aryl-2,1-benzisoxazoles and acetophenones without the use of acid or base promoters and the whole process is complete within 1–2 h at room temperature. Thus, our method for the preparation of 2,4-diarylquinolines has advantages such as being a one-pot process from easily accessible and inexpensive starting materials and much milder reaction conditions. In addition, considering the differences with respect to the reaction conditions used in our method and in Ref. 1b, it is safe to say that in our process the substance involved in the reaction towards ketones could not be 2-aminobenzophenone itself. It may be an intermediate formed in situ through SmI_2 induced reductive cleavage of the N–O bond in 3-aryl-2,1-benzisoxazoles.[10] It is the much higher reactivity of this intermediate that allows the condensation process in our method to be accomplished under much milder conditions compared with using 2-aminobenzophenone as the substrates.

In conclusion, with high yields, mild and neutral conditions as well as easily accessible starting materials,[15] the present work may provide a useful method for the preparation of 2-aminobenzophenones and 2,4-diarylquinolines from 3-aryl-2,1-benzisoxazoles.[16,17] Further studies to clarify the mechanism of this process and to develop other new uses of 3-aryl-2,1-benzisoxazoles as intermediates in organic synthesis are now in progress in our laboratory.

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16. General procedure for the preparation of 2-aminobenzophenones (**2**): Under anhydrous conditions, a mixture of powdered samarium (0.15 g, 1 mmol) and iodine (0.25 g, 1 mmol) in dry THF (20 mL) was stirred at room temperature until the samarium disappeared. To the resulting dark blue suspension of SmI_2 was added 3-aryl-2,1-benzisoxazole (0.5 mmol). The mixture was stirred at room temperature for 5 min. On completion, the reaction mixture was poured into H_2O (10 mL) and extracted with ethyl acetate (3×15 mL). The combined extracts were washed subsequently with a saturated solution of $Na_2S_2O_3$ (15 mL) and a saturated solution of NaCl (15 mL) and dried over anhydrous Na_2SO_4. After evaporating the solvent under reduced pressure, the crude product was purified by preparative TLC on silica gel using ethyl acetate–cyclohexane (1:4) as eluent to yield the corresponding 2-aminobenzophenones. All the 2-aminobenzophenones are known compounds and have physical data (mp) and spectral characteristics (IR and ^{1}H NMR) in agreement with those of the known compounds.
17. Typical procedure for the preparation of 5-chloro-2-(4-methylphenyl)-4-phenylquinoline (**4b**): To a dark blue suspension of SmI_2 (1 mmol) in THF was added 3-phenyl-5-chloro-2,1-benzisoxazole (0.12 g, 0.5 mmol). The mixture was stirred at room temperature for 5 min. Then, to the reaction mixture was added 4′-methylacetophenone (0.72 g, 0.6 mmol). Stirring was continued for another hour. On completion, the reaction mixture was poured into H_2O (15 mL) and extracted with diethyl ether (3×15 mL). The combined extracts were washed with a saturated solution of $Na_2S_2O_3$ (15 mL) and a saturated solution of NaCl (15 mL) and dried over anhydrous Na_2SO_4. After evaporating the solvent under reduced pressure, the crude product was purified by preparative TLC on silica gel using ethyl acetate–cyclohexane (1:8) as eluent to yield **4b** (66%), mp 132–134°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, 1H, J=8.0 Hz), 8.09 (d, 2H, J=8.0 Hz), 7.85 (d, 1H, J=3.5 Hz), 7.82 (s, 1H), 7.67–7.64 (m, 1H), 7.57–7.52 (m, 5H), 7.33 (d, 2H, J=8.0 Hz), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 119.9, 124.5 126.5, 127.4 128.7, 128.8 129.5, 129.6, 130.4, 131.7, 131.9, 136.4, 137.9, 139.8, 147.3, 148.3, 157.1; MS m/z (%): 329 (M^+, 100), 294 (23). Anal. calcd for $C_{22}H_{16}ClN$: C, 80.11; H, 4.89; N, 4.25. Found: C, 80.25; H, 4.78; N, 4.33%. Other 2,4-diarylquinoline derivatives were obtained in a similar manner and were also fully characterized by IR, ^{1}H NMR, ^{13}C NMR, MS and elemental analysis.