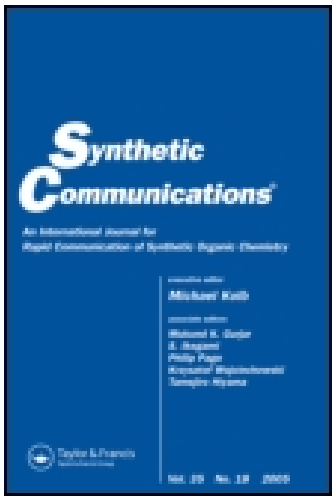

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FACILE SYNTHESIS OF 2-SUBSTITUTED-QUINAZOLIN-4-(3H)-ONES PROMOTED BY SmI_2

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FACILE SYNTHESIS OF 2-SUBSTITUTED-QUINAZOLIN-4-(3H)-ONES PROMOTED BY SmI_2

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ABSTRACT

Mediated by SmI_2, 2-substituted-quinazolin-4-(3H)-ones are readily accessible in fair yields by reaction of *N,N*-diethyl-*o*-nitrobenzamide with appropriate aryl and benzyl nitriles.

The chemistry of samarium (II) iodide (SmI_2) is of current interest in organic synthesis (1–6). Since its introduction by Kagan and his group, SmI_2 has been extensively investigated as a mild, neutral, selective, versatile, and ether-soluble one-electron transfer reductant in synthetic chemistry (7). Barbier reactions (8,9), Reformatsky reactions (10,11), the homocoupling allylic or benzylic halides (12,13), acid chlorides, (14), carbonyl compounds (15,16), the reduction of organohalo compounds (17,18), etc., have been reported using SmI_2 as a reagent. The reactivity of SmI_2 toward various nitrogen compounds including nitro coupounds (19–21), azo coupounds (22), hydrazones (20,23), oximes (20), imines (20), azides (24–26), and hydroxylamines (27) has been examined. The cyano group, however, is more stable to samarium diiodide than is a nitro group and could not be reduced by this reagent. Souppe and Kagan (20) reported that aromatic and

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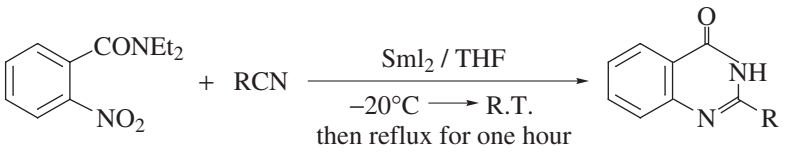
aliphatic nitriles are inert in the presence of SmI_2, and *m*- or *p*-nitrobenzonitrile could be selectively reduced to the corresponding cyanoanilines in almost quantitative yields.

Quinazolin-4-(3H)-ones or the tautomeric hydroxyquinazolines, especially their 2-aryl or alkyl derivatives, are a class of fused heterocycles of considerable interest due to the remarkable diversity of their biological activities (28). Indeed, some of these compounds possess soporofic, diuretic, and antiinflammatory properties, and may be further modified in the construction of new pharmaceutical entities (29). Unfortunately, synthetic methods for the elaboration of this bicyclic system of rather simple structure are not general in scope, and involve multistep, and often low-yielding, reaction sequences. The main synthetic approaches to such compounds consist of preliminary amidation of 2-aminobenzonitrile (30), 2-aminobenzoic acid (28), or ethyl 2-aminobenzoate (31). The oxidative ring closure of intermediates under acidic conditions affords the quinazolinones in various yields (32). The compounds are also accessible by aza-Wittig reactions from α-azido-substituted aromatic imides (33,34) or from aromatic iminophosphoranes and isocyanates (35). Different one-step syntheses have been described, but the condensation of 2-aminobenzoic acid with amides (36), thioamides (37), or nitriles requires either high temperatures or must be affected in a sealed tube at 200°C (38).

Here we report a novel method for the synthesis of 2-aryl and 2-benzyl-quinazolin-4-(3H)-ones (Sch. 1). Table 1 summarizes our results on the reaction of *N*,*N*-diethyl-*o*-nitrobenzamide and appropriate aromatic and benzyl nitriles with SmI_2 to give 2-aryl and 2-benzyl-quinazolin-4-(3H)-ones in fair yields. However, *N*,*N*-diethyl-*o*-nitrobenzamide failed to react with acetonitrile to give a similar product under the same conditions. We found that the results were satisfactory when two substrates were treated with SmI_2 in dry THF under −20°C at the beginning of reactions.

In conclusion, we believe that the above work provides a useful method for the preparation of 2-substituted-quinazolin-4-(3H)-ones. The remarkable advantages of this reaction are neutral and mild reaction conditions and simple operation. Further studies to synthesize these types of compounds using SmI_2 are now in progress in our laboratory.



Scheme 1.

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Table 1.

Entry	R	Yield (%)[a]
1a	Ph	68
1b	$PhCH_2$	61
1c	*m*-$CH_3C_6H_4$	63
1d	*p*-ClC_6H_4	75
1e	3,4-$(OCH_2O)C_6H_3$	58
1f	2,4-dichloroC_6H_3	55
1g	*p*-$MeOC_6H_4$	64
1h	*p*-$CH_3C_6H_4$	63
1i	CH_3	0[b]

[a]*N*,*N*-diethyl-*o*-nitrobenzamide 1 mmol, nitriles 1.5 mmol, SmI_2 6 mmol were used. Yields based on *N*,*N*-diethyl-*o*-nitrobenzamide.
[b]the reaction was studied under 0°C, 20°C, and refluxing conditions.

EXPERIMENTAL

Tetrahydrofuran was distilled from sodium benzophenone immediately prior to use. All reactions were conducted under a nitrogen atomsphere. Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC 80 instrument as DMSO-d_6 solutions using TMS as internal standard. IR spectra were determined on a PE-683 spectrometer. Mass spectra were obtained on a HP 5989A mass spectrometer using electron-impact mode (70 eV). Elemental analyses were performed on a Carlo Erba 1106 instrument. Metallic samarium and all solvents were purchased from commercial sources, without further purification before use.

General Procedure for the Syntheses of 2-Substituted-Quinazolin-4-(3H)-Ones. A solution of *N*,*N*-diethyl-*o*-nitrobenzamide (39) (1 mmol) and nitriles (1.5 mmol) in anhydrous THF (5 mL) was added dropwise to a solution of SmI_2 (6 mmol) in THF (40 mL) at −20°C under a nitrogen atomsphere. The mixture is allowed to reach r.t., then refluxed for 1 h. After cooling, THF was distilled under reduced pressure. Water (10 mL) was added and the pH of the mixture was then adjusted to 5–6 by addition of HCL (0.1 *N*). the mixture was extracted with EtOAc (3 × 30 mL), washed with diluted brine, filtered, and evaporated under reduced pressure. The crude product was washed with EtOH, then H_2O, to give the product.

1a: m.p. 234–236°C (lit. (31) 236°C; υ_{max} (KBr)/cm^{-1} 1660; δ_H (DMSO-d_6), 12.5 (1H, s), 7.5–8.3 (9H, m).

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1b: m.p. 257–258°C. (lit. (31) 256°C); υ_{max} (KBr)/cm^{-1} 1655; δ_H (DMSO-d_6) 12.4 (1H, s), 7.5–8.2 (9H, m), 4.0 (2H, s).

1c: m.p. 210–212°C (lit. (29) 212°C); υ_{max} (KBr)/cm^{-1} 1660; δ_H (DMSO-d_6) 12.5 (1H, s), 7.4–8.2 (8H, m), 2.4 (1H,s).

1d: m.p. 305–306°C (lit. (40) 306°C); υ_{max} (KBr)/cm^{-1} 1670; δ_H (DMSO-d_6) 12.8 (1H, s), 7.7–8.4 (8H, m).

1e: m.p. 245–247°C (lit. (29) 246°C); υ_{max} (KBr)/cm^{-1} 1650; δ_H (DMSO-d_6) 12.4 (1H, s), 7.2–8.2 (8H, m), 6.0 (1H, s).

1f: m.p. 248–250°C; υ_{max} (KBr)/ cm^{-1} 1680; δ_H (DMSO-d_6) 12.6 (1H, s), 7.7–8.4 (7H, m) m/z 292 ($M^+ + 2$, 26), 290 (M^+, 41), 119 (100%); Anal. for $C_{14}H_8N_2OCl_2$: Cal. (found) C, 57.76 (57.78); H, 2.77 (2.65); N, 9.62 (9.53)%.

1g: m.p. 247–248°C (lit. (31) 247°C); υ_{max} (KBr)/cm^{-1} 1660; δ_H (DMSO-d_6) 12.4 (1H, s), 7.1–8.2 (8H, m), 3.8 (3H, s).

1h: m.p. 241°C (lit. (31) 241°C); υ_{max} (KBr)cm/$^{-1}$ 1670; δ_H (DMSO-d_6) 12.5 (1H, s), 7.4–8.2 (8H, m), 2.3 (1H, s).

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