SmI_2-mediated reduction of phenacyl azides: a novel preparation of 2,4-diarylpyrroles

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A novel reductive cyclisation of phenacyl azides brought about by samarium iodide is described in this paper. By this process several 2,4-diarylpyrroles have been prepared.

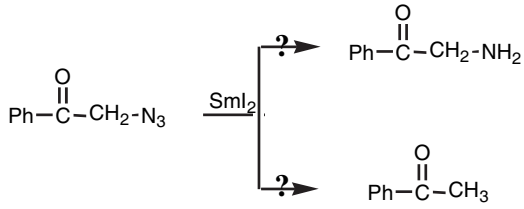
Keywords: phenacyl azides, pyrroles, samarium(II) iodide

Pyrroles are very widespread heterocyclic structural motifs among medicinally significant natural and unnatural products, and feature strongly in the design of conducting polymers, molecular optics, or sensors and devices.[1] Consequently, the efficient assembly of this class of molecule is a significant objective in synthetic chemistry.[2] Usually, the construction of the pyrrole ring system involves a multi-step approach from pre-formed intermediates. In addition, most of the available methods lead to pyrroles which are substituted at various positions with functional groups, and thus require further synthetic operations to afford simple alkyl or aryl substituted pyrroles. In particular, synthetic routes to simple 2,4-diaryl pyrroles are limited,[3] and convenient procedures for preparing 2,4-diarylpyrroles with substituents on the aryl rings are even more rare.[3e]

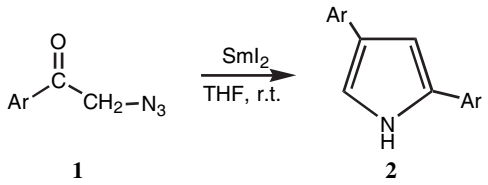
It is well known that samarium(II) iodide has played a significant role in promoting reductive reactions, and the reactivity of SmI_2 towards various nitrogen-containing organic compounds has been well examined.[4] It has been demonstrated that, upon treatment with samarium (II) iodide, alkyl, aryl or aroyl azides can readily be transformed into the corresponding primary amines or amides.[5] It has also been reported that samarium (II) iodide can efficiently promote the reduction of σ-hetero-substituted ketones to give back the corresponding ketones.[6] As part of our comprehensive program pursuing more applications of samarium(II) iodide as a reducing agent in organic synthesis, we speculated that, on treatment with samarium(II) iodide, phenacyl azides would either be reduced to the corresponding σ-amino-substituted acetophenone, or undergo C–N bond cleavage to give the acetophenone itself (Scheme 1). However, subsequent investigation revealed a novel and unexpected reductive cyclisation dimerisation reaction of phenacyl azides in the presence of samarium(II) iodide, and thereby 2,4-diarylpyrrole rings were readily constructed in a very mild manner (Scheme 2).[7]

Our exploration of this transformation began with phenacyl azide (1, Ar = Ph, Scheme 2). It was found that when 1a was treated with a solution of 2.5 equiv of SmI_2 in THF at room temperature under a nitrogen atmosphere, the deep blue colour of SmI_2 changed to yellow immediately. A few minutes later, TLC analysis indicated that the starting azide had been completely consumed and a new product had been formed. Subsequent separation and purification gave a solid product whose physical and spectral data showed that, instead of the proposed products shown in Scheme 1, an unexpected structure, namely 2,4-diphenylpyrrole, had been formed.

The scope of the above reductive process was further investigated by extending the substrate to other phenacyl azide derivatives. As summarised in Table 1, an array of phenacyl azide derivatives was suitable for this pyrrole formation process. It turned out that all of the substrates in



Scheme 1



1 **2**

Scheme 2

Table 1 underwent the transformation smoothly and afforded 2,4-diarylpyrroles in fair yields. Phenacyl azides bearing both electron-donating groups (4-Me and 4-OMe, Table 1, entries 2–3) and electron withdrawing groups (4-Br and 4-Cl, entries 4–5,) underwent almost equally smooth reductive cyclisation process under the same conditions. The absence of an observable substituent effect demonstrates the generality of this method as a novel alternative for the preparation of 2,4-diarylpyrroles bearing various substituents on the aryl rings.

Although the detailed mechanism of the reaction has not been clarified, a plausible mechanism based on the literature for the formation of 2,4-diarylpyrroles is shown in Scheme 3. Firstly, the cleavage of the $C–N_3$ bond may take place through two SET (single electron transfer) processes, in which SmI_2 donates two electrons successively and leads to the corresponding enolate (**a**).[8] Then **a** abstracts a proton from another substrate molecule (**1**) to afford a new enolate (**b**) and acetophenone (**3**). By losing a N_2 molecule, **b** is then transformed into anion **c**. As a strong base, **c** can abstract a proton from **3** to afford the phenylglyoxalimine intermediate (**d**) and **a**. Reaction of **d** with a followed by loss of two

Table 1 Reduction of phenacyl azides mediated by SmI_2

Entry	Ar	Reaction time/min	Product	Yield/%[a]
1	C_6H_5	5	**2a**	72
2	4-$CH_3C_6H_4$	5	**2b**	70
3	4-$CH_3OC_6H_4$	5	**2c**	65
4	4-BrC_6H_4	5	**2d**	76
5	4-ClC_6H_4	5	**2e**	75
6	2-naphthyl	10	**2f**	56

[a]Isolated yields based on phenacyl azides.

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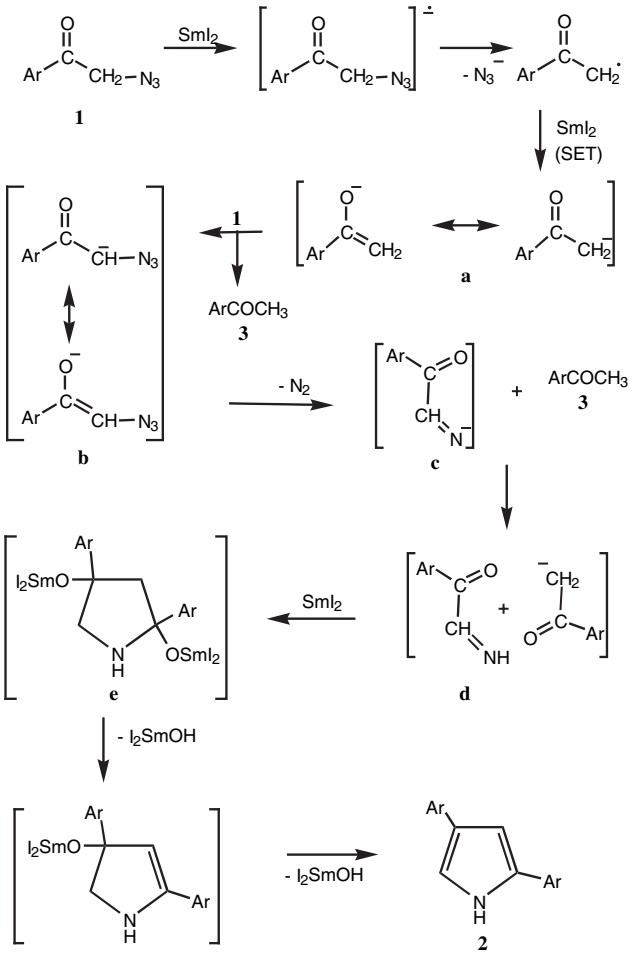


Scheme 3

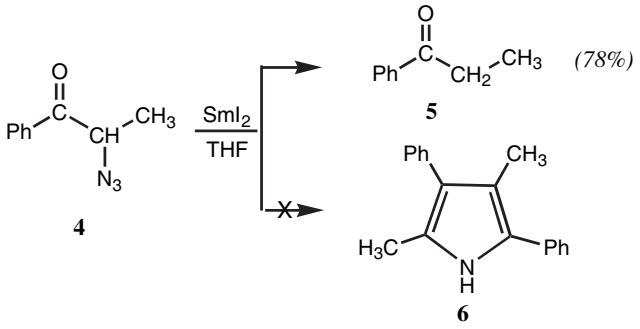
$HOSmI_2$ fragments successively from intermediate **e** can give the 2,4-diarylpyrrole (**2**) as the final product. However, alternative routes to intermediate **d** cannot be eliminated

Finally, in the hope of obtaining 2,3,4,5-tetrasubstituted pyrroles by the above reductive cyclisation process, the reduction of 2-azidopropiophenone (**4**) was investigated (Scheme 4). However, on treatment with SmI_2, **4** underwent a reductive C–N bond cleavage to give propiophenone (**5**) rather than the desired 3,5-dimethyl-2,4-diphenylpyrrole (**6**). This result may be due to the additional steric hindrance resulted from the extra methyl group attached to the σ carbon atom in **4** compared with **1**.

In conclusion, we have described here a novel reductive cyclisation of phenacyl azides promoted by SmI_2. Through this process, several 2,4-diarylpyrrole derivatives were obtained. With its reasonable yields, mild and neutral conditions, as well as easily accessible starting materials, the procedure presented here may provide a useful alternative for the preparation of pyrrole derivatives. Further studies to develop other new uses of SmI_2 as an efficient promoter in organic synthesis are now in progress in our laboratory.

Experimental

Tetrahydrofuran was distilled from sodium-benzophenone immediately prior to use. All reactions were conducted under a nitrogen atmosphere. Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC-400 instrument as DMSO-d_6 or $CDCl_3$ solutions using TMS as an internal standard. IR spectra were taken as KBr discs with a Bruker Vector-22 infrared spectrometer. Mass spectra were obtained by a HP-5989B mass spectrometer. Elemental analyses were performed on an EA-1110 instrument. Metallic samarium and all solvents were purchased from commercial



Scheme 4

sources and were used without further purification. The starting material phenacyl azides 1 were prepared according to the published method.[9]

General procedure for the preparation of 2,4-diarylpyrroles (**2a–f**)
A solution of phenacyl azide (1 mmol) in dry THF (3 ml) was added dropwise to the solution of SmI_2 (2.5 mmol) in THF (20 ml) at room temperature under a nitrogen atmosphere. The deep blue colour of the solution changed to yellow immediately. After being stirred for about 5 minutes, the reaction mixture was quenched with dilute HCl (0.1 mol/l, 3 ml) and extracted with ether (3 × 20 ml). The organic phase was successively washed with saturated aqueous $Na_2S_2O_3$ (10 ml) and then saturated brine (10 ml), and was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude product, which was purified by preparative TLC using ethyl acetate and cyclohexane (1 : 6) as eluant.

2,4-Diphenylpyrrole (**2a**): M.p. 166-169 °C (lit.[3a] 166–170 °C). IR (KBr): ν 3350 cm^{-1} (NH). ^{1}H NMR (400 MHz, DMSO): δ 6.95 (t, 1H, *J* = 2 Hz), 7.10–7.19 (m, 2H), 7.30–7.39 (m, 5H), 7.61 (d, 2H, *J* =7.2 Hz), 7.68 (d, 2H, *J* = 7.6 Hz), 11.3 (bs, 1H, NH). MS: *m/z* (%) 219 (M^+, 100), 191 (13), 116 (17), 115 (21), 89 (6), 77 (5).

2,4-Bis-(4-methylphenyl)pyrrole (**2b**): M.p. 214–216 °C (lit.[3a] 224 °C). IR (KBr): ν 3345 cm^{-1} (NH). ^{1}H NMR (400 MHz, DMSO): δ 2.28 (s, 3H), 2.29 (s, 3H), 6.84 (t, 1H, *J* = 2 Hz), 7.12 (d, 2H, *J* = 7.8 Hz), 7.17 (d, 2H, *J* = 7.2 Hz), 7.24 (t, 1H, *J* = 2 Hz), 7.48 (d, 2H, *J* = 7.8 Hz), 7.56 (d, 2H, *J* = 7.8 Hz), 11.4 (br s, 1H, NH). MS: *m/z* (%) 247 (M^+, 100). Anal. Calcd for $C_{18}H_{17}N$: C, 87.41; H, 6.93; N, 5.66. Found: C, 87.45; H, 6.97; N, 5.64 %.

2,4-Bis-(4-methoxyphenyl)pyrrole (**2c**): M.p. 186–189 °C. IR (KBr) ν 3355 cm^{-1} (NH). ^{1}H NMR (400 MHz, DMSO): δ 3.89 (s, 3H), 3.90 (s, 3H), 6.65 (t, 1H, *J* = 2 Hz), 6.92 (d, 2H, *J* = 7.8 Hz), 7.08 (d, 2H, *J* = 7.2 Hz), 7.15 (t, 1H, *J* = 2 Hz), 7.30 (d, 2H, *J* = 7.8 Hz), 7.38 (d, 2H, *J* = 7.8 Hz), 11.2 (br s, 1H, NH). MS: *m/z* (%) 279 (M^+, 100). Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.45; H, 6.09; N, 5.04 %.

2,4-Bis-(4-bromophenyl)pyrrole (**2d**): M.p. 224–226 °C. IR (KBr): ν 3340 cm^{-1} (NH). ^{1}H NMR (400 MHz, DMSO): δ 7.03 (s, 1H), 7.43 (s, 1H), 7.49 (d, 2H, *J* = 8.4 Hz), 7.54–7.58 (m, 4H), 7.63 (d, 2H, *J* = 8.4 Hz), 11.6 (br s, 1H, NH). MS: *m/z* (%) 379 (50) 377 (100), 375 (53) (M^+). Anal. Calcd for $C_{16}H_{11}Br_2N$: C, 50.96; H, 2.94; N, 3.71. Found: C, 50.95; H, 2.97; N, 3.68 %.

2,4-Bis-(4-chlorophenyl)pyrrole (**2e**): M.p. 193–194 °C (lit.[3a] 196 °C). IR (KBr): ν 3338 cm^{-1} (NH). ^{1}H NMR (400 MHz, DMSO) δ 7.01 (t, 1H, *J* = 2 Hz), 7.36 (d, 2H, *J* = 8.4 Hz), 7.42–7.43 (m, 3H), 7.63 (d, 2H, *J* = 8.4 Hz), 7.72 (d, 2H, *J* = 8.4 Hz), 11.6 (br s, 1H, NH); MS: *m/z* (%) 287 (M^+, 100). Anal. Calcd for $C_{16}H_{11}Cl_2N$: C, 66.69; H, 3.85; N, 4.86. Found: C, 66.65; H, 3.87; N, 4.88 %.

2,4-Di-(2-naphthyl)pyrrole (**2f**): M.p. 190–192 °C. IR (KBr): ν 3340 cm^{-1} (NH). ^{1}H NMR (400 MHz, DMSO): δ 6.68 (s, 1H), 7.05 (s, 1H), 7.33–7.39 (m, 4H), 7.58–7.80 (m, 10H), 11.5 (bs, 1H, NH). MS: *m/z* (%): 319 (M^+, 100). Anal. Calcd for $C_{24}H_{17}N$: C, 90.25; H, 5.36; N, 4.39. Found: C, 90.33; H, 5.20; N, 4.33 %.

SmI_2 reduction of 2-azidopropiophenone (**4**): A solution of 2-azidopropiophenone (**4**, 1 mmol) in dry THF (3 ml) was added dropwise to a solution of SmI_2 (2.5 mmol) in THF (10 ml) at room temperature under a nitrogen atmosphere. The deep blue colour of the solution changed into yellow immediately. At completion (5 min, monitored by TLC), the reaction mixture was quenched with dilute HCl (0.1 mol/l, 3 ml) and extracted with ether (3 × 20 ml). The organic phase was washed successively with saturated aqueous $Na_2S_2O_3$ (10 ml) and saturated brine (10 ml), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give

the crude product, which was purified by preparative TLC to give propiophenone (5, 78%).

Propiophenone (**5**): Oil. IR (KBr): ν 1710 cm^{-1} (C=O). ^1H NMR (400 MHz, $CDCl_3$): δ 1.22 (t, 3H, *J* = 6.4 Hz), 2.96 (d, 2H, *J* = 6.4 Hz), 7.40–7.54 (m, 3H), 7.93–7.95 (m, 2H).

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