Tetrahedron Letters 51 (2010) 868–871

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Practical method for synthesis of 2,3-disubstituted indole derivatives promoted by β-(benzotriazol-1-yl)allylic *O*-stannyl ketyl radicals

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ARTICLE INFO

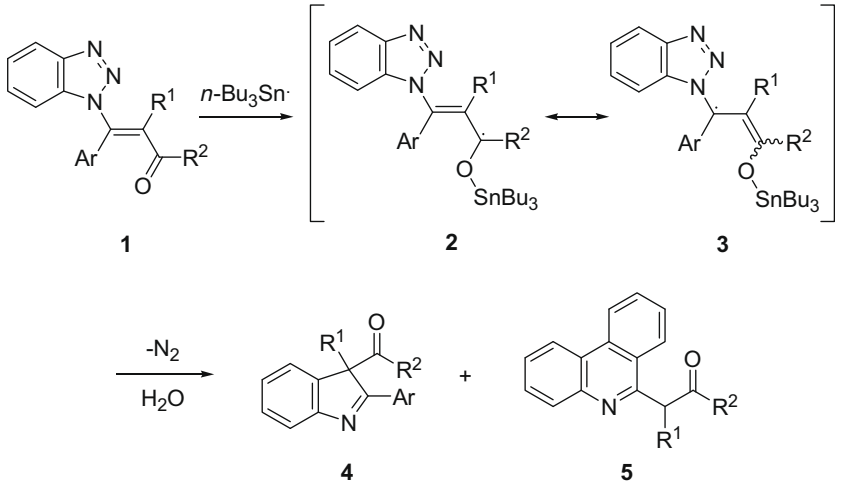
Article history:
Received 17 October 2009
Revised 4 December 2009
Accepted 8 December 2009
Available online 11 December 2009

ABSTRACT

Treatment of β-aryl-β-(benzotriazol-1-yl)-α-primary alkyl (or aryl)-α,β-unsaturated ketones **1** with *n*-Bu_3SnH (4 equiv) in a catalytic amount of AIBN in PhH at reflux afforded 3-alkyl (or aryl)-2-arylindoles **8** in good yields. However, when *tert*-butyl group is bonded at α-position, 3-acyl (or aroyl)-2-arylindoles **9** were obtained as major products along with phenanthridines **5** as minor products.

Radical cyclizations by *n*-Bu_3SnH have attracted considerable interest. The reactions of halides, alkenes, alkynes, sulfides, and selenides that contain a suitably situated radical acceptor with *n*-Bu_3SnH can be utilized to produce cyclization products.[1] In particular Enholm and Kinter[2] have shown, among others that the reaction of tributyltin radical with α,β-unsaturated carbonyl undergoes free radical cyclizations to give substituted cyclopentane rings and bicyclo[3,3,0]ring systems. Similarly, the reaction of aldehyde with tributyltin radical was reported to undergo 5- or 6-*exo* radical cyclization yielding cyclic alcohol via *O*-stannyl ketyl radical.[3]

In continuation of our study on exploring the utility of benzotriazole as an synthetic auxiliary,[4] we became interested in the generation of β-(benzotriazol-1-yl)allylic *O*-stannyl ketyl radical **2**, because its canonical form **3**, aryl(benzotriazol-1-yl)[β-(*O*-stannyl)vinyl]methyl radical, is structurally analogous to diaryl(benzotriazol-1-yl)methyl radical reported.[5] And the radical **2** could be readily generated in one step by treatment of **1** with tributyltin



Scheme 1.

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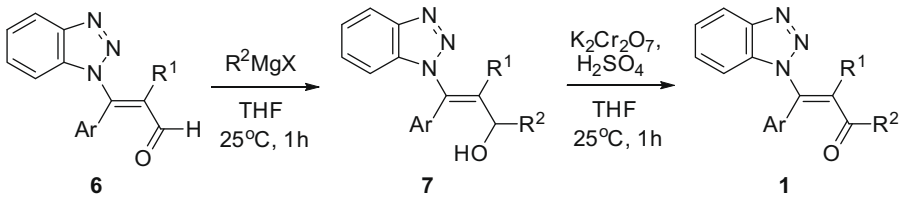
doi:10.1016/j.tetlet.2009.12.030



Scheme 2.

Table 1
Yields of products **1** and **7**, and the ratio of the stereoisomers

	Ar	R^1	R^2	Yield[a] (%)	
				7 (*E*:*Z*)[b]	**1** (*E*:*Z*)[b]
a	Ph	Ph	Me	90 (1.21:1)	87 (1.28:1)
b	Ph	Ph	Ph	90 (2.97:1)	88 (2.86:1)
c	Ph	Ph	1-Naphthyl	77 (1.45:1)	82 (1.56:1)
d	Ph	Me	Ph	73 (3.12:1)	79 (2.91:1)
e	Ph	2-Furyl	Ph	80 (2.22:1)	81 (2.44:1)
f	3-MeC_6H_4	Ph	Ph	87 (3.29:1)	85 (3.08:1)
g	3-MeC_6H_4	2-Naphthyl	Ph	85 (3.16:1)	89 (2.94:1)
h	3-MeC_6H_4	2-Thienyl	Ph	80 (6.17:1)	82 (4.83:1)
i	2,3-$Me_2C_6H_3$	4-MeC_6H_4	Ph	84 (2.68:1)	89 (2.84:1)
j	4-FC_6H_4	Ph	Ph	89 (1.97:1)	81 (1.89:1)
k	Ph	*t*-Bu	Me	86 (6.01:1)	78 (5.31:1)
l	Ph	*t*-Bu	Ph	92[c]	82[c]
m	Ph	*t*-Bu	1-Naphthyl	71[c]	84[c]
n	Ph	*t*-Bu	2-Thienyl	85[c]	83[c]
o	2-MeC_6H_4	*t*-Bu	Ph	83 (7.07:1)	84[d]
p	2,5-$Me_2C_6H_3$	*t*-Bu	Ph	80 (5.93:1)	82[e]
q	4-$MeOC_6H_4$	*t*-Bu	Me	89 (2.77:1)	84 (2.78:1)
r	4-$MeOC_6H_4$	*t*-Bu	4-$MeOC_6H_4$	71[c]	78[c]

[a] Isolated yields.
[b] The ratios of stereoisomers were determined based on the ^1H NMR (300 MHz, $CDCl_3$) spectroscopic data.
[c] (*E*)-isomer only.
[d] Yield of (*E*)-**1o** from pure (*E*)-**7o**.
[e] Yield of (*E*)-**1p** from pure (*E*)-**7p**.

radical whereas the reported radical was generated by lithiation of diaryl(benzotriazol-1-yl)methanes followed by addition of iodine in two steps. Furthermore, the applicability of the radical generated according to the literature method, organic synthesis does not appear to be promising despite the existence of the mechanistic significance. The radical **3** could be expected to induce the ring opening by loss of nitrogen, and the subsequent by cyclization to give indole derivatives **4** as well as phenanthridine derivatives **5**, if any, as in a fashion to diaryl(benzotriazol-1-yl)methyl radical (Scheme 1).

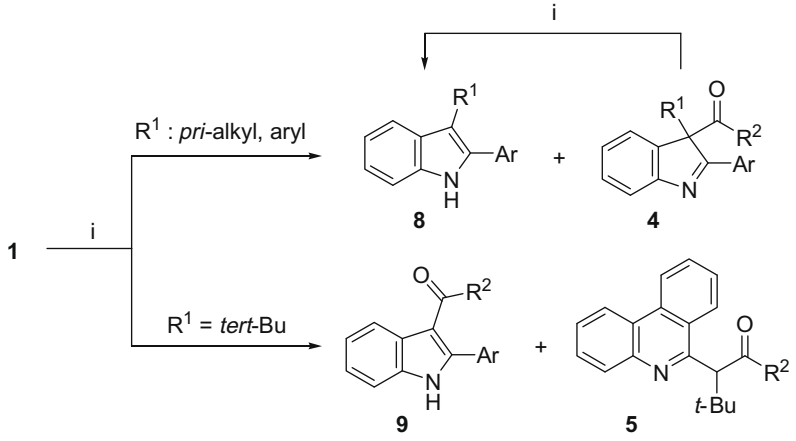
We report now a novel method for the title compounds using benzotriazole as a synthetic auxiliary in this Letter. Compound **1** (Scheme 2) was prepared by Grignard reaction followed by oxidation reaction of 2,3-disubstituted-3-(benzotriazol-1-yl)propanal **6** whose synthesis was previously described.[4a] Yields of **1** and **7** along with the (*E*)/(*Z*) ratios are summarized in Table 1.

Treatment of **1f** (Ar = 3-MeC_6H_4, $R^1 = R^2$ = Ph) with *n*-Bu_3SnH (1.0 equiv) in the presence of azobisisobutyronitrile (AIBN) (0.5 equiv) in PhH for 2 h at reflux gave 2-(3-methylphenyl)-3-phenylindole **8f** (Ar = 3-MeC_6H_4, R^1 = Ph) and 2-(3-methylphenyl)-3-benzoyl-3-phenyl-3*H*-indole **4f** (Ar = 3-MeC_6H_4, $R^1 = R^2$ = Ph) in 38% and 44% yields, respectively[6] (Scheme 3). Upon increasing the concentration of *n*-Bu_3SnH (2.5 equiv) under the same conditions, the yield of **8f** increased to 79% at the expense of that of **4f** (10%). A further increase of *n*-Bu_3SnH (4.0 equiv) resulted in a yield of **8f** to 86% and no **4f** was detected. In addition, compound **4f** was converted to compound **8f** in 92% yield using *n*-Bu_3SnH under the same foregoing conditions.

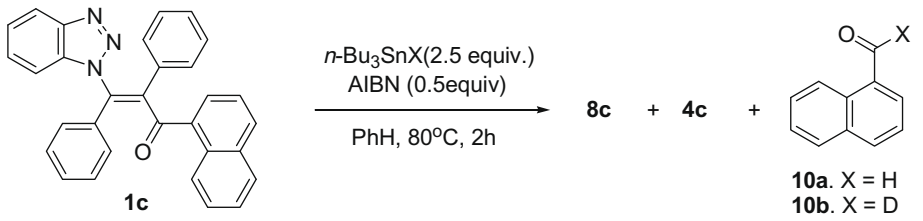
To find the locus of the R^2CO moiety detached in the course of the conversion from **4** to **8**, the selected compound **1c** (Ar = R^1 = Ph, R^2 = 1-naphthyl) was subjected to the same conditions as described in expectation of a solid by-product (Scheme 4). From the reaction using *n*-Bu_3SnH were isolated **8c**, **4c**, and 1-naphthaldehyde **10a** (X = H) in 76%, 11%, and 52% yields, respectively, along with a small amount of *n*-hexabutylditin, whose structure was confirmed on the basis of the ^1H NMR spectroscopy. When *n*-Bu_3SnD was used, we obtained the same products, and α-deuterio-naphthalene-1-carbaldehyde (**10b**) instead of **10a**.

In the meantime, R^1 = *t*-Bu, 3-acyl (or aroyl)-2-arylindoles **9** together with a significant amount of phenanthridines **5** were isolated. Yields of compounds **5**, **8**, and **9** are summarized in Table 2.

The formation of the products **4**, **5**, **8**, and **9** may be initiated by the generation of β-(benzotriazol-1-yl)allylic *O*-stannyl ketyl radical **2** whose canonical form **3** undergoes the ring opening by loss of nitrogen to give *N*-α,β-unsaturated alkylidenaminophenyl radical



Scheme 3. Reagents and conditions: (i) *n*-Bu_3SnH (2.5 equiv), AIBN (0.5 equiv), PhH, 80 °C, 2 h.

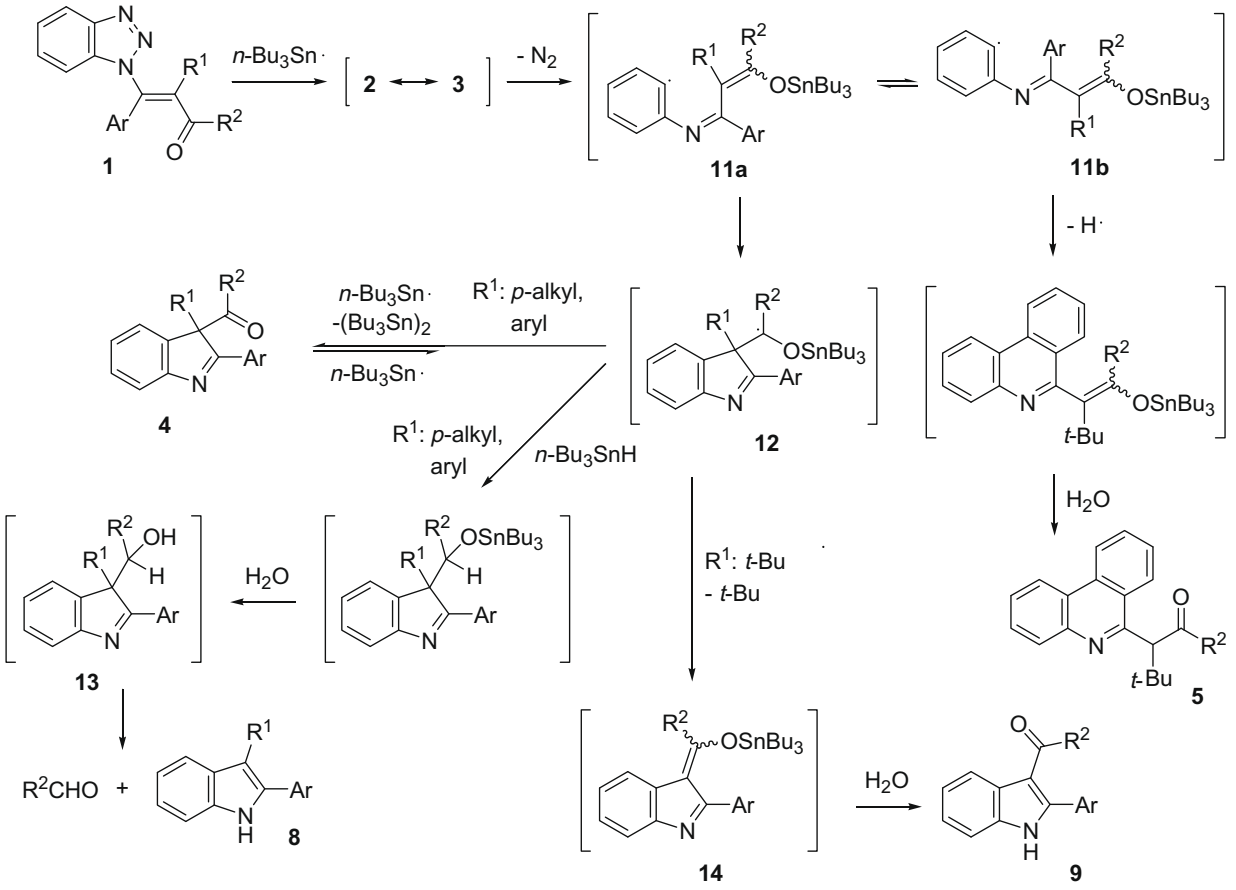


Scheme 4.

comprising a mixture of conformational isomers **11a** and **11b** because of the occurrence of a rapid inversion of the imino nitrogen (Scheme 5). The intramolecular cyclization of the conformer **11a** would afford an *O*-stannyl ketyl radical **12**, which is reverted to compound **4** by loss of *n*-Bu_3Sn·. Alternatively the ketyl radical **12** abstracts a hydrogen atom followed by hydrolysis to give an intermediate alcohol **13**, which rapidly undergoes an oxidative C–C bond cleavage to give compound **8** and aldehyde (R^2CHO). An attempt was made to prepare **13** (Ar = R^1 = Ph, R^2 = 1-naphthyl) by treating compound **4c** with $NaBH_4$ (2 equiv) in EtOH for 15 min at room temperature. However, only compound **8c** was isolated in 91% yield. None of the desired alcohol was detected. The result suggests that compound having the structure analogous to the intermediate **13** is very unstable. No literature precedents have been found. Consequently the reactions give compound **8** as major products in the presence of excess amount of *n*-Bu_3SnH. On the other hand, when R^1 = *t*-Bu, the *O*-stannyl ketyl radical **12** is envisaged to readily extrude *tert*-butyl radical to produce 3-alkyliden-3*H*-indolin **14**, which undergoes hydrolysis, compounds **5** may be formed by an intramolecular aromatic radical substitution reaction of the conformer **11b** followed by hydrolysis.

Consequently, the reactions give compounds **8** as major products in the presence of excess amount of *n*-Bu_3SnH. On the other hand, when R^1 = *t*-Bu, the *O*-stannyl ketyl radical **12** is envisaged to readily extrude *tert*-butyl radical to produce 3-alkyliden-3*H*-indolin **14**, which undergoes hydrolysis, compounds **5** may be formed by an intramolecular aromatic radical substitution reaction of the conformer **11b** followed by hydrolysis. It is interesting to note that compounds **5** were isolated only in the cases where R^1 = *t*-Bu. Moreover, with Ar bearing one *ortho* substituent, yields of **5o** (20%) and **5p** (trace) were comparable to that of **5l** (27%) bearing no *ortho* substituent. The result may be ascribed to the steric bulkiness of the *tert*-butyl group which causes the equilibrium concentration of **11b** to be significant to avoid the steric repulsion arising from the bulky *tert*-butyl group and the phenyl radical.

In summary, β-(benzotriazol-1-yl)allylic *O*-stannyl ketyl radical produced from β-aryl-β-(benzotriazol-1-yl)-α-primary alkyl (or aryl)-α,β-unsaturated ketones can be utilized as precursors for



Scheme 5.

Table 2
Yields of compounds **5**, **8**, and **9**

	Ar	R^1	R^2	Yield[a] (%)		
				8	**9**	**5**
a	Ph	Ph	Me	85[7]		
b	Ph	Ph	Ph	75[7,b]		
c	Ph	Ph	1-Naphthyl	76[7,b]		
d	Ph	Me	Ph	71[8,b]		
e	Ph	2-Furyl	Ph	84		
f	3-MeC_6H_4	Ph	Ph	86		
g	3-MeC_6H_4	2-Naphthyl	Ph	87		
h	3-MeC_6H_4	2-Thienyl	Ph	90		
i	2,3-$Me_2C_6H_3$	4-MeC_6H_4	Ph	81		
j	4-FC_6H_4	Ph	Ph	89[9]		
k	Ph	*t*-Bu	Me		73[10]	16
l	Ph	*t*-Bu	Ph		67[11]	27
m	Ph	*t*-Bu	1-Naphthyl		61	30
n	Ph	*t*-Bu	2-Thienyl		64	28
o	2-MeC_6H_4	*t*-Bu	Ph		69	20
p	2,5-$Me_2C_6H_3$	*t*-Bu	Ph		74	—[c]
q	4-$MeOC_6H_4$	*t*-Bu	Me		75[12]	13
r	4-$MeOC_6H_4$	*t*-Bu	4-$MeOC_6H_4$		66	25

[a] Isolated yields when *n*-Bu_3SnH (4.0 equiv) was used.
[b] When *n*-Bu_3SnH (2.5 equiv) was used, not only compound **8b–d** but also compounds **4b** (Ar = R^1 = R^2 = Ph, 13%) and **4c** (Ar = R^1 = Ph, R^2 = 1-naphthyl, 11%) were isolated. However, no **4d** (Ar = R^2 = Ph, R^1 = Me) was formed.
[c] Trace (it was not isolated.)

the synthesis of 3-alkyl (and aryl)-2-arylindoles and 3-acyl (and aroyl)-2-arylindoles.

Acknowledgments

This work was supported by the S.N.U. foundation of Overhead Research Fund and Kolon Life Science Inc. Spectroscopic data were obtained from the Korea Basic Science Institute, Seoul branch.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.030.

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6. *Typical procedure*: To a solution of **1f** (130 mg, 0.31 mmol) in benzene (20 mL) were added *n*-Bu_3SnH (91 mg, 0.31 mmol) and AIBN (25 mg, 0.16 mmol) at room temperature. The mixture was heated for 2 h at reflux followed by addition of water (30 mL) and was extracted with CH_2Cl_2 (20 mL × 3). The combined organic extracts were dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was chromatographed on a silica gel column (70–230 mesh, 3 × 10 cm, EtOAc/*n*-hexane = 1:7) to give compound **8f** (33 mg, 38%): mp 109–111 °C (*n*-hexane); IR (KBr) 3378, 3046, 3023, 2911, 1602, 1500, 1454, 1332, 1243, 1012, 769, 701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.40 (s, 3H, CH_3), 7.15–7.26 (m, 4H, ArH), 7.31–7.42 (m, 3H, ArH), 7.45–7.57 (m, 5H, ArH), 7.80 (d, *J* = 7.8 Hz, 1H, ArH), 8.27 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 22.0, 111.4, 115.4, 120.1, 120.9, 123.1, 126.0, 126.7, 128.9, 129.0, 129.1, 129.2, 130.7, 133.1, 134.8, 135.7, 136.3, 138.8. Anal. Calcd for $C_{21}H_{17}N$: C, 89.01; H, 6.05; N, 4.94. Found: C, 88.95; H, 6.11; N, 5.08 and **4f** (52 mg, 44%): mp 152–154 °C (EtOAc/*n*-hexane); IR (KBr) 3058, 2921, 2854, 1673, 1596, 1525, 1446, 1268, 1203, 1147, 848, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.34 (s, 3H, CH_3), 7.13 (t, *J* = 8.3 Hz, 2H, ArH), 7.18–7.30 (m, 7H, ArH), 7.31–7.37 (m, 4H, ArH), 7.41 (d, *J* = 7.5 Hz, 1H, ArH), 7.45 (t, *J* = 7.5 Hz, 1H, ArH), 7.60–7.65 (m, 1H, ArH), 7.84 (d, *J* = 7.7 Hz, 1H, ArH), 7.96 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 21.8, 78.6, 122.3, 124.1, 127.3, 127.5, 128.0, 128.4, 128.7, 128.8, 129.0, 129.7, 129.8, 132.6, 133.0, 133.1, 137.7, 138.4, 138.8, 142.9, 155.8, 178.7, 197.0 (signal of one aromatic C atom not visible). Anal. Calcd for $C_{28}H_{21}NO$: C, 86.79; H, 5.46; N, 3.61; O, 4.13. Found: C, 86.92; H, 5.52; N, 3.52.
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