Tetrahedron Letters 51 (2010) 4275–4277

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Base-promoted selective β-fragmentation of homoallylamines

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ARTICLE INFO

Article history:
Received 23 March 2010
Revised 3 June 2010
Accepted 8 June 2010
Available online 11 June 2010

ABSTRACT

A selective β-fragmentation of homoallylamines with the combination of iodobenzene diacetate, iodine, and sodium acetate is reported. The desired carbon–carbon bond cleavage proceeded via a radical β-scission pathway under mild conditions with good functional group tolerance.

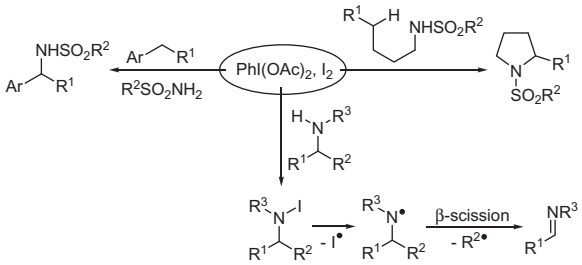
The selective cleavage of saturated carbon–carbon bonds is a topic of interest in organic synthesis.[1,2] β-Scission of alcohols under radical conditions has been thoroughly investigated and widely used to provide a simple and classic way to a wide range of compounds.[3,4] β-Scission of cycloalkyloxyl radicals with small ring size leads to the ring opening to yield medium- and large-sized carbon- and hetero-cycles.[5] For the alkoxyl radicals with an adjacent functionality, the β-scission gives rise to stable carbon radicals, which are ready to be oxidized and trapped by nucleophiles.[6] However, to the best of our knowledge, compared to the extensive studies on the alkoxyl radical fragmentation (ARF), carbon–carbon β-scission of amines has been a particularly elusive reaction and received much less scrutiny.

In our previous papers, we have reported the intra- and intermolecular amination of sp^3 C–H bonds with sulfonamides with the combination of $PhI(OAc)_2$ and I_2 under the transition-metal-free conditions.[7] Sulfonamidyl radicals,[8] which are generated from the reactions of sulfonamides with acetyl hypoiodite,[9] are proposed as the reactive intermediates. With the aim of extending this approach, we investigated the β-scission of sulfonamidyl radicals (Scheme 1).

Preliminary survey was carried out under the Suárez cleavage conditions (2 equiv of $PhI(OAc)_2$ and 1 equiv of I_2 in $Cl(CH_2)_2Cl$ at room temperature) and various *N*-Ts amines were examined (Scheme 2).[10] The formation of sulfonimine **11a** was only observed in the reaction of *N*-Ts homoallylamine **10a**, albeit in a low yield (6% yield, determined by the ^1H NMR spectroscopy of the unpurified reaction mixture). Additionally, the reaction afforded an unexpected cyclization product **12**, which was assigned as 3-iodo-5-phenyl-1-tosylpyrrolidin-2-yl acetate, in 31% yield. Its structure and relative stereochemistry were unambiguously established by its single-crystal diffraction analysis (Fig. 1).

The preliminary results indicated that the β-scission of homoallylamine is particularly favorable due to the generation of a stable allylic radical (Scheme 3). However, the allyl group is also reactive to acetyl hypoiodite to give rise to an iodoacetoxylation product **II**. In the presence of another molecular acetyl hypoiodite, intermediate **II** is further converted into the corresponding sulfonamidyl radical **III**, which is ready to undergo the subsequent 1,5-H migration, oxidation, and cyclization to afford 3-iodo-5-phenyl-1-tosylpyrrolidin-2-yl acetate **12**.

Based on the analysis of reaction pathway, we supposed that acids (HOAc and HI), which were generated in the reaction, might protonate the amine group of substrate to inhibit the formation of sulfonamidyl radical **I**. To verify our hypothesis, a set of experiments were carried out. When 1 equiv of AcOH was added, no sulfonimine was detected (Table 1, entry 1). On the contrary, the presence of an inorganic base promoted the formation of sulfonimine (Table 1, entries 2–4). With the addition of 2 equiv of NaOAc, the yield of **11a** increased to 28%. Due to their sensitivity to the oxidative conditions, organic bases were not good to the reaction (Table 1, entries 5 and 6). Although lower temperatures slowed down the reaction (5 min at 25 °C, 30 min at 0 °C, 75 min at −10 °C), the yield of **11a** was dramatically improved to 65% when the reaction was carried out at 0 °C (Table 1, entry 7). A longer reaction time resulted in the decomposition of sulfonimine (Table 1, entry 9). The



Scheme 1.

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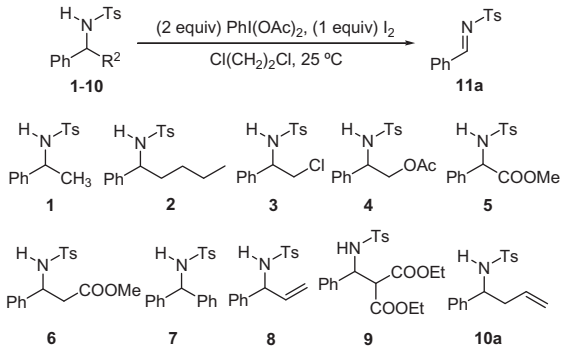
doi:10.1016/j.tetlet.2010.06.031



Scheme 2. β-Scission of *N*-Ts amines.

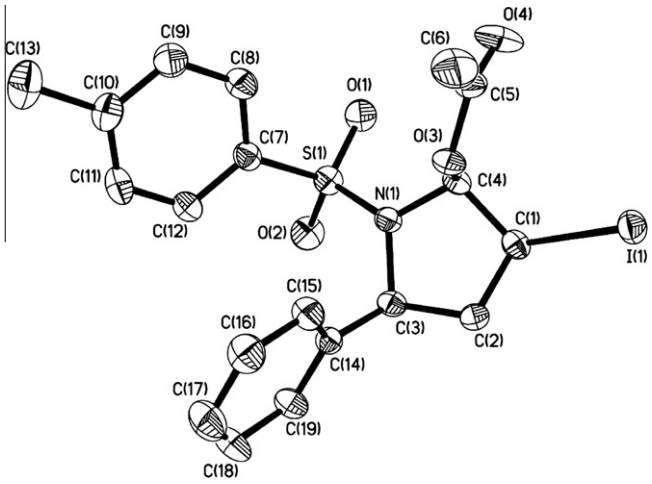
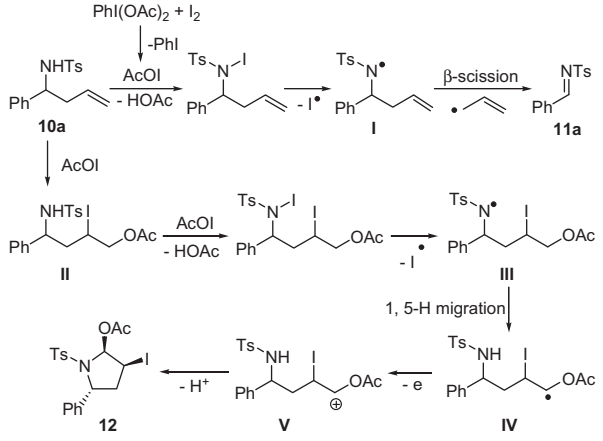


Figure 1. X-ray diffraction structure of **12**.

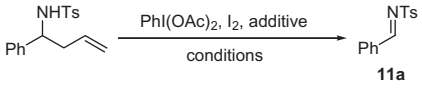


Scheme 3. A plausible reaction pathway.

amounts of reagents were optimized (Table 1, entries 10–17). The best ratio of substrate, AcONa, $PhI(OAc)_2$, and I_2 was 1:1:1:0.5, with which the yield of 1 increased to 81%. Sulfonimine also was formed in CH_2Cl_2, toluene, and CH_3CN, but not in MeOH and DMF (Table 1, entries 18–22).

While homoallylic benzenesulfonamides were effective substrates for the β-scission, the reactions of some other sulfonylamides and amides did not afford any sulfonimines (Table 2, entries 1–7).[11] The reaction was found to tolerate a range of different substituents with different electronic demands on the aromatic rings involving electron withdrawing and electron donating (Table 2, entries 8–15). The position of the substituent had an influence

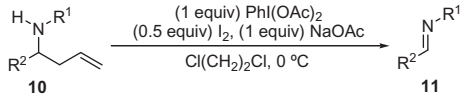
Table 1
Evaluation of reaction conditions[a]



Entry	DIB (equiv)	I_2 (equiv)	Additive (equiv)	Conditions	**11a**[b] (%)
1	2	1	HOAc (1)	$Cl(CH_2)_2Cl$, 25 °C	0
2	2	1	NaOAc (2)	$Cl(CH_2)_2Cl$, 25 °C	28
3	2	1	K_2CO_3 (2)	$Cl(CH_2)_2Cl$, 25 °C	21
4	2	1	*t*-BuOK (2)	$Cl(CH_2)_2Cl$, 25 °C	23
5	2	1	DBU (2)	$Cl(CH_2)_2Cl$, 25 °C	0
6	2	1	Et_3N (2)	$Cl(CH_2)_2Cl$, 25 °C	0
7	2	1	NaOAc (2)	$Cl(CH_2)_2Cl$, 0 °C	65
8	2	1	NaOAc (2)	$Cl(CH_2)_2Cl$, −10 °C	41
9	2	1	NaOAc (2)	$Cl(CH_2)_2Cl$, 0 °C	12[c]
10	2	1	NaOAc (3)	$Cl(CH_2)_2Cl$, 0 °C	55
11	2	1	NaOAc (1)	$Cl(CH_2)_2Cl$, 0 °C	73
12	2	1	NaOAc (0.5)	$Cl(CH_2)_2Cl$, 0 °C	48
13	3	1	NaOAc (1)	$Cl(CH_2)_2Cl$, 0 °C	46
14	1	1	NaOAc (1)	$Cl(CH_2)_2Cl$, 0 °C	73
15	0.5	1	NaOAc (1)	$Cl(CH_2)_2Cl$, 0 °C	43
16	1	2	NaOAc (1)	$Cl(CH_2)_2Cl$, 0 °C	25
17	1	0.5	NaOAc (1)	$Cl(CH_2)_2Cl$, 0 °C	81
18	1	0.5	NaOAc (1)	CH_2Cl_2, 0 °C	56
19	1	0.5	NaOAc (1)	Toluene, 0 °C	18
20	1	0.5	NaOAc (1)	CH_3CN, 0 °C	41
21	1	0.5	NaOAc (1)	MeOH, 0 °C	0
22	1	0.5	NaOAc (1)	DMF, 0 °C	0

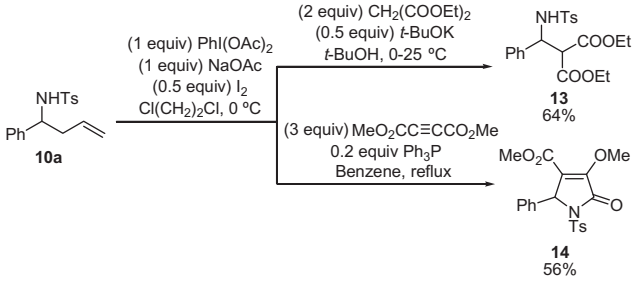
[a] The reactions were performed with **10a** (0.2 mmol), $PhI(OAc)_2$, I_2, and additive (as noted) in solvent (1 mL).
[b] Yields were determined by the ^1H NMR spectroscopy of the unpurified reaction mixture with $Br(CH_2)_2Br$ as the standard.
[c] The reaction was stirred at 0 °C for 2 h.

Table 2
β-Scission of homoallylamines[a]



Entry	R^2	R^1	**11**	Yield[b] (%)
1	C_6H_5	Ts	**11a**	75
2	C_6H_5	$PhSO_2$	**11b**	71
3	C_6H_5	CH_3SO_2	**11c**	—
4	C_6H_5	CF_3SO_2	**11d**	—
5	C_6H_5	*tert*-$BuSO_2$	**11e**	—
6	C_6H_5	PhCO	**11f**	—
7	C_6H_5	CF_3CO	**11g**	—
8	*p*-CH_3O–C_6H_4	Ts	**11h**	60
9	*o,m*-Di-CH_3O–C_6H_3	Ts	**11i**	50
10	*p*-CH_3–C_6H_4	Ts	**11j**	61
11	*p*-F–C_6H_4	Ts	**11k**	58
12	*p*-Br–C_6H_4	Ts	**11i**	63
13	*p*-Cl–C_6H_4	Ts	**11m**	66
14	*o*-Cl–C_6H_4	Ts	**11n**	30
15	1-Naphthyl	Ts	**11o**	71
16	2-Furan	Ts	**11p**	50
17	2-Thiophen	Ts	**11q**	83
18	2-Pyridin	Ts	**11r**	—
19	*i*-Bu	Ts	**11s**	—
20	*t*-Bu	Ts	**11t**	—

[a] The reactions were performed with substrate **10** (2 mmol), $PhI(OAc)_2$ (2 mmol), I_2 (1 mmol), and NaOAc (2 mmol) in anhydrous $Cl(CH_2)_2Cl$ (10 mL).
[b] Isolated yields.



Scheme 4.

on the yields of sulfonimines. For example, reaction of *p*-chloro substituted substrate gave rise to sulfonimine **11m** in 66% yield, while reaction of *o*-chloro-substituted substrate afforded the corresponding product **11n** in 30% yield. With respect to the hetaryl substrates (Table 2, entries 16–18), 1-furan-2-yl and 1-thiophen-2-yl homoallylamines are suitable substrates in this process and the desired products were isolated in moderate to good yields, while no sulfonimine was obtained for the reaction of 1-pyridin-2-yl homoallylamine. When enolizable or nonenolizable aliphatic derivatives were employed under the conditions, no sulfonimines were detected (Table 2, entries 19 and 20). However, the analysis of the unpurified reaction mixtures by ^{1}H NMR spectroscopy indicated the generation of $TsNH_2$ and the corresponding aldehydes.

The aryl *N*-sulfonylimines formed in the β-scission reactions were ready to undergo subsequent reactions with diethyl malonate and dimethyl acetylenedicarboxylate without further purification (Scheme 4).

In conclusion, we have described a selective base-promoted β-fragmentation of homoallylamines with the combination of iodobenzene diacetate with iodine. The desired carbon–carbon bond cleavage proceeded via a radical β-scission pathway under mild conditions with good functional group tolerance. Further studies on the application of this system are ongoing and will be reported in due course.

Acknowledgments

Financial support from National Natural Science Foundation of China (20702006) and Fudan University is gratefully acknowledged.

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11. *General experimental procedure and spectroscopic data*: A Schlenk tube with stir bar was charged with homoallylic benzenesulfonamide (2 mmol), $PhI(OAc)_2$ (644 mg, 2 mmol), and NaOAc (164 mg, 2 mmol). The tube was evacuated and back-filled with argon, and then $Cl(CH_2)_2Cl$ (10 mL) and I_2 (254 mg, 1 mmol) were added. The reaction mixture was allowed to stir at 0 °C until substrate disappeared monitored by TLC. The reaction was quenched with saturated $Na_2S_2O_3$, and the reaction mixture was extracted by ethyl acetate (50 mL × 3). The organic layer was dried over Na_2SO_4, concentrated, and purified by recrystallization (hexane/ethyl acetate) to provide the desired product. *N*-Benzylidene-4-methylbenzenesulfonamide **11a** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1H), 7.88–7.94 (m, 4H), 7.62 (t, J = 7.5 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 2.44 (s, 3H).