Novel Synthesis of 2-Aminobenzimidazoles from Isoselenocyanates

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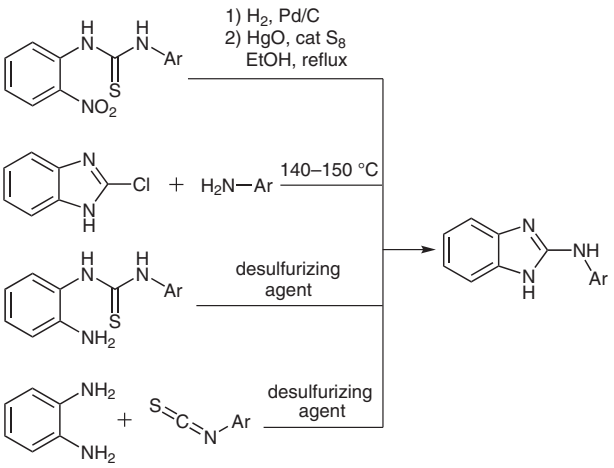
Abstract: An efficient one-pot procedure for the synthesis of 2-aminobenzimidazoles from isoselenocyanates and various substituted diamines is described. Precipitation of elemental selenium from the reaction mixture greatly simplifies the purification procedure and also allows it to be re-used for preparation of isoselenocyanates. A possible mechanism for the formation of 2-aminobenzimidazoles is proposed.

Key words: 2-aminobenzimidazoles, isoselenocyanates, cyclization, selenium recycling

Benzimidazole is an important structural unit in medicinal chemistry, which comprises nearly one-quarter of the top-100-selling drugs.[1] Specifically, 2-aminobenzimidazoles can be found in a number of biologically active molecules used as antiviral, antihistamine, and anticancer agents.[2] Therefore, the synthesis of 2-aminobenzimidazoles has attracted considerable interest.



Scheme 1 Conventional routes to 2-aminobenzimidazole

Conventional routes for the preparation of 2-aminobenzimidazoles include: i) cyclization of nitrothioureas; ii) S_NAr reaction of chlorobenzimidazole; iii) cyclization of aminothioureas; iv) one-pot cyclization of diamines and isothiocyanates (Scheme 1). Method (i) often gives poor yield during the reduction of nitro group, while method (ii) requires elevated temperature and usually yields self-arylation products.[3] Since 1999, method (iii) has been the preferred method to 2-aminobenzimidazole, as it can give relatively high overall yield of products. The most frequently used desulfurizing agents[4] are HgO, $HgCl_2$, CuCl, MeI, tosyl chloride, dicyclohexylcarbodiimide, diisopropylcarbodiimide, *N*-(3-dimethyl-aminopropyl)-*N*′-ethyl-carbodiimide hydrochloride. To simplify this process, one-pot synthesis from diamines and isothiocyanates has been developed [method (iv)]. Carbodiimide reagents, especially polymer-supported carbodiimides serve as ideal desulfurizing agents.[5]

As our interests in selenium chemistry and consistent efforts in developing parallel reaction with isoselenocyanates, we herein report our latest result: an one-pot procedure to prepare 2-aminobenzimidazoles using isoselenocyanates and various substituted diamines. We found that solid selenium precipitated in the reaction without any deselenizing agent.

Isoselenocyanates were generally introduced as key materials for the preparation of selenium-containing heterocycles.[6] Fernández-Bolaños's group developed a procedure for the preparation of unprotected glycopyranosyl selenoureas from isoselenocyanates. The selenoureas were further converted into bicyclic isoureas with precipitation of elemental selenium.[7]

Table 1 Optimization of the Reaction Conditions[a]

Entry	Solvents	Temp (°C)	Time (h)[b]	Yields (%)[c]
1	DMF	50	4	86
2	DMF	70	4	91
3	DMF	120	4	90
4	THF	reflux	16	82
5	pyridine	70	6	80
6	MeCN	reflux	12	65
7	toluene	70	24	–
8	CH_2Cl_2	reflux	24	–
9	$CHCl_3$	reflux	24	–
10	EtOAc	70	24	–

[a] 1-Isoselenocyanato-4-methoxybenzene (1 mmol) and benzene-1,2-diamine (1 mmol).
[b] Monitored by TLC, until selenourea is fully consumed.
[c] Isolated yield by column chromatography.

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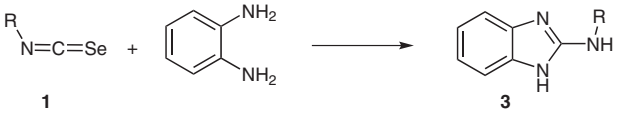
Similar phenomenon was observed in our experiment that the element selenium precipitated when we treated isoselenocyanate with diamine in DMF. TLC analysis detected the formation of 2-aminobenzimidazole, which was identified by both NMR and MS analyses (Scheme 2).

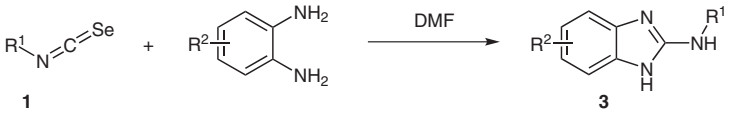


Scheme 2 A new route to 2-aminobenzimidazole

Encouraged by this result, we proceeded to find out the most favorable reaction conditions. As shown in Table 1, DMF was the best reaction solvent. After the optimization of reaction conditions, we explored the scope of this reaction by changing the substrates. A variety of functionalized 2-aminobenzimidazoles were then obtained by this method (Table 2). Both electron-donating and electron-withdrawing groups on phenyl isoselenocyanates were well tolerated in this reaction. However, phenyl isoselenocyanates with electron-withdrawing groups gave the products in better yields and the reaction completed in shorter time. The *ortho*-substituted isoselenocyanate (Table 2, entries 3 and 4) gave relatively lower yields due to the steric hindrance effect. Alkyl-substituted isoselenocyanate also gave good product yields.

The procedure could also be applied to structurally diverse 1,2-phenylenediamine. Both electron-donating and electron-withdrawing groups on 1,2-phenylenediamine provided the corresponding 2-aminobenzimidazoles in good yields (Table 2, entry 10–15). Unfortunately, the desired products were not obtained by treating cyclohexane-1,2-diamine or propane-1,2-diamine with isoselenocyanates. Compared with the previous reported methodologies,[4] this method has several advantages such as higher product yields, shorter reaction time, and milder reaction conditions. Since the solid selenium could precipitate from the reaction medium in nearly quantitative amount (typical recovery was 95–97%), it could be used for the preparation of isoselenocyanates following Koketsu's procedure.[8]

Table 2 Preparation of 2-Aminobenzimidazole[a]

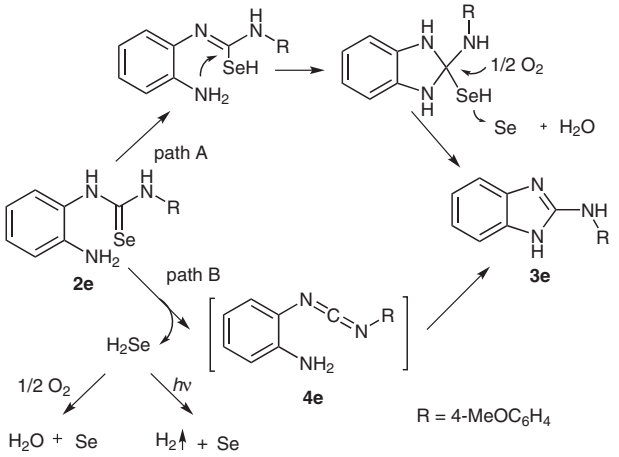


Entry	R^1	R^2	Product	Time(h)	Yield (%)[b]
1	Ph	H	3a	6	83
2	3-MeC_6H_4	H	**3b**	4	91
3	2-MeC_6H_4	H	**3c**	6	85
4	2-EtC_6H_4	H	**3d**	6	83
5	4-$MeOC_6H_4$	H	**3e**	4	90, 89[c]
6	4-ClC_6H_4	H	**3f**	2	95
7	4-BrC_6H_4	H	**3g**	2	94
8	1-naphthyl	H	**3h**	8	81
9	cyclohexyl	H	**3i**	6	85
10	4-$MeOC_6H_4$	4-O_2N	**3j**	12	75
11	4-ClC_6H_4	4-O_2N	**3k**	12	77
12	4-$MeOC_6H_4$	4-Me	**3l**	6	81
13	4-ClC_6H_4	4-Me	**3m**	6	82
14	4-$MeOC_6H_4$	4-Cl	**3n**	10	72
15	4-ClC_6H_4	4-Cl	**3o**	10	79
16	Ph	propane-1,2-diamine	–	24	–
17	Ph	cyclohexane-1,2-diamine	–	24	–

[a] Monitored by TLC, until selenourea is fully consumed.
[b] Isolated yield by column chromatography.
[c] Using reproduced 1-isoselenocyanato-4-methoxybenzene.

Two possible reaction pathways are proposed in Scheme 3. Path A includes an oxygen-participated cyclization of selenourea, thereafter elemental selenium is generated to give 2-aminobenzimidazole. Path B starts with the decomposition of selenourea to give H_2Se and corresponding carbodiimide, which then cyclized to 2-amino-benzimidazole. H_2Se then underwent photolysis[9] or oxidation[10] to yield element selenium.

In order to determine the reaction pathway of the whole process, a control experiment was performed. First, a suspension of 1-(2-aminophenyl)-3-(4-methoxyphenyl) selenourea (**2e**) prepared previously[11] in DMF was heated up to 70 °C in an opened vessel. Two other experiments were carried out simultaneously.[12] The first reaction was performed in a nitrogen-protected vessel while the second reaction was carried out in a light-avoiding but non-nitrogen-protected vessel.



Scheme 3 Possible pathways of the reaction

In the case of normal reaction conditions[13] and light-avoiding control, the reaction completed in 4 hours, 2-aminophenylselenourea **2e** was totally completely reacted and 2-aminobenzimidazole **3e** and element selenium were formed. However, no selenium was observed in nitrogen atmosphere control (only a trace of **3e** detected by TLC) even with longer reaction time of 36 hours. The significant difference of conversion ratios obtained in the normal conditions, light-avoiding control and nitrogen-atmosphere control suggested oxygen was crucial to this reaction. If path B was the main pathway of this reaction, 2-aminophenylselenourea **2e** should have decomposed and converted into compound **4e** and hydrogen selenide in nitrogen. Moreover, compound **4e** is not stable and would transform to **3e** immediately. However, only trace amount of **3e** was detected, which meant that path B was not the main pathway. In contrast, path A seems to be more reasonable as the main pathway.

In summary, we have successfully developed a one-pot procedure for 2-aminobenzimidazoles and avoided the isolation of intermediate selenourea. In contrast to conventional methods, isoselenocyanates were firstly used in this route as the key reagents. The precipitation of element selenium largely simplifies the purification procedures. Meanwhile, the starting material isoselenocyanates can be prepared by using the recovered element selenium to avoid pollution problems.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(11) **Typical Procedure for Compound 2e**
A mixture of 1-isoselenocyanato-4-methoxybenzene (**1e**; 0.212 g, 1 mmol) and phenylene-1,2-diamine (0.108 g, 1 mmol) were suspended in $CHCl_3$ (20 mL). The reaction was carried out at r.t. After 10 min the reaction was ceased, and the reaction mixture was concentrated under vacuum. The residue was washed with a mixture of hexane and EtOAc (hexane–EtOAc = 20:1) to obtain 1-(2-aminophenyl)-3-(4-methoxyphenyl) selenourea (**2e**) as a yellow solid (0.313 g,

98% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.63 (s, 1 H), 9.34 (s, 1 H), 7.26–7.29 (m, 2 H), 6.96–7.02 (m, 2 H), 6.87–6.90 (m, 2 H), 6.74 (dd, 1 H, *J* = 1.2, 8.0 Hz), 6.56 (dt, 1 H, *J* = 1.6, 7.6 Hz), 4.89 (s, 2 H), 3.74 (s, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 178.8, 157.0, 143.9, 132.5, 128.2, 127.4, 127.0, 124.4, 116.4, 115.9, 113.5, 55.2. HRMS (EI): *m/z* calcd for $C_{14}H_{15}N_3OSe$: 320.0302; found: 320.0317.

(12) **Procedure for Controlled Experiment**

1-(2-aminophenyl)-3-(4-methoxyphenyl) selenourea (**2e**, 1 mmol) was suspended in DMF (20 mL) with magnetic stirring. The reaction was carried out at 70 °C. A light-avoiding control and a nitrogen-atmosphere control reaction were set up at the same time. The reaction was monitored by TLC. 2-Aminophenylselenourea was totally converted into **3e** after 4 h in normal and light-avoiding control. The reaction in nitrogen atmosphere was prolonged to 36 h, but only trace of **3e** was found.

(13) **Typical Procedure for Compound 3e**

A mixture of 1-isoselenocyanato-4-methoxybenzene (**1e**; 0.212 g, 1 mmol) and phenylene-1,2-diamine (0.108 g, 1 mmol) was suspended in DMF (20 mL). The reaction vessel was heat to 70 °C with magnetic stirring. Tracing by TLC, the reaction completed when selenourea **2e** disappeared. The reaction mixture was then cooled to r.t. and filtered to separate solid selenium. The solid selenium was washed by EtOAc (10 mL). The combined filtrate was concentrated under vacuum, and the residue was purified by column chromatography on silica gel (hexane–EtOAc = 1:1). A white solid *N*-(4-methoxyphenyl)-1*H*-benzo[*d*]imidazol-2-amine (**3e**, 0.215 g, 90% yield), was then obtained. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.79 (s, 1 H), 9.15 (s, 1 H), 7.65 (d, 2 H, *J* = 8.8 Hz), 7.26 (s, 2 H), 6.95–6.96 (m, 2 H), 6.91 (d, 2 H, *J* = 9.2 Hz), 3.73 (s, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6 + $CDCl_3$): δ = 154.1, 151.7, 138.0, 133.9, 119.8, 119.5, 114.0, 112.2, 55.1. ESI-MS: *m/z* = 240 $[M + H]^+$.