A Facile Method for Preparation of Optically Active Hydantoin

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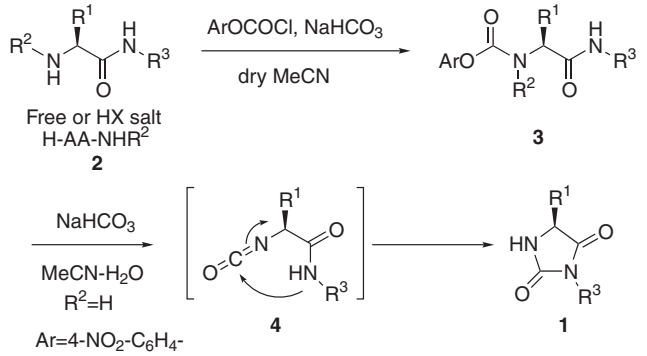
Treatment of *N*-(4-nitrophenoxycarbonyl)amino acid amide, which was prepared from amino acid amide and 4-nitrophenyl chloroformate, under weakly basic conditions proceeded to afford the corresponding hydantoin. A direct conversion of amino acid amide into hydantoin without isolation of *N*-(4-nitophenoxycarbonyl)amino acid amide was also accomplished.

Hydantoins and their synthesis by the action of carbonyl compounds have been known since early in the 20th century.[1] Recently, it has been found that hydantoins play an important role in medicinal activities such as fibrinogen receptor antagonist and leukocyte function-associated antigen-1 (LFA-1) antagonist.[2] Therefore, many synthetic methods have been reported in the past 10 years and can be classified into two types: 1) cyclization of *N*-carbamoyl amino acid ester under basic or acidic conditions,[3] 2) cyclization of *N*-alkoxy or phenoxycarbonyl amino acid amide.[4] However, racemization check of the synthesized hydantoin has hardly been reported.

4-Nitrophenyl *N*-substituted carbamates[5,6] as well as 4-nitrophenyl esters[7] and carbonates[8] are known as activated esters and react with amines to produce ureas, carboxamides, and carbamates, respectively. Among them, 4-nitrophenyl *N*-substituted carbamates generate the corresponding isocyanates on treatment with alkali or amine.[9] From the above reports, we expected that treatment of *N*-(4-nitrophenoxycarbonyl)amine bearing a nucleophilic group with alkaline would generate the corresponding isocyanate, which will transform into the corresponding cyclic compound by its intramolecular cyclization. In this communication, we wish to report a convenient method for preparation of (*S*)-hydantoin (**1**) from (*S*)-amino acid amide (**2**) via formation of *N*-(4-nitrophenoxycarbonyl)amino acid amide (**3**) under weakly basic conditions (Scheme 1).

According to the method for the preparation of 4-nitrophenyl carbamate,[5] (*S*)-**3** was prepared by reaction of (*S*)-**2** with 4-nitrophenyl chloroformate in the presence of 2.0 equimolar amounts of $NaHCO_3$ in dry MeCN at room temperature for 3 h (Table 1).[10] Unfortunately, because it was difficult to purify (*S*)-**3** from a small amount of 4-nitrophenol by chromatography on silica-gel, (*S*)-**3** was isolated by reprecipitation with ethyl acetate-hexane only. Therefore, the yields of (*S*)-**3** remained moderate.



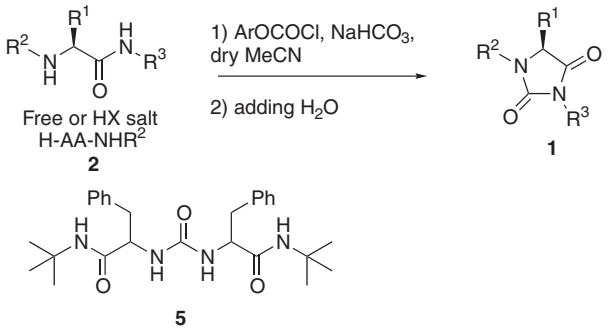
Scheme 1.

Table 1. Preparation of (*S*)-**3** from (*S*)-**2**

Run	R^1	R^2	R^3	Substrate	Product	Yield/%
1	CH_2Ph	H	H	**2a**[a]	**3a**	84
2	CH_2Ph	H	Ph	**2b**[a]	**3b**	76
3	CH_2Ph	H	$(CH_2)_2Ph$	**2c**[b]	**3c**	71
4	$-(CH_2)_3-$		Ph	**2d**[a]	**3d**	78

[a]HCl salt. [b]4-Toluenesulfonic acid salt.

Next, we examined the degradation of (*S*)-**3** under basic conditions to prepare (*S*)-**1**. It was found that treatment of **3** with 1.0 equimolar amount of $NaHCO_3$ in H_2O-MeCN at room temperature for 3 h afforded (*S*)-**1** (Table 2). All of the reaction mixture changed from colorless into yellow instantly when an aqueous $NaHCO_3$ was added to a MeCN solution of (*S*)-**3**. This phenomenon shows that degradation of (*S*)-**3** and generation of 4-nitrophenol are very fast. Since formation of the corresponding isocyanate of (*S*)-**3d** derived from proline is impossible, we suspected that no transformation of (*S*)-**3d** into (*S*)-**1d** proceeded. Although the reaction rate was slow, (*S*)-**1d** was obtained. This fact indicated that (*S*)-**1d** would be given in another reaction pathway.



Scheme 2.

Table 2. Transformation of (*S*)-**3** into (*S*)-hydantoin (**1**)

Run	R^1	R^2	R^3	Substrate	Product	Yield/%[a]
1	CH_2Ph	H	H	**3a**	**1a**	92
2	CH_2Ph	H	Ph	**3b**	**1b**	99
3	CH_2Ph	H	$(CH_2)_2Ph$	**3c**	**1c**	93
4	$-(CH_2)_3-$		Ph	**3d**	**1d**	80[b]

[a]The structures of these compounds were supported by IR, Mass, and ^1H NMR spectra. [b]The starting material (**3d**) was recovered in 14% yield.

In comparing the reaction conditions of 4-nitrophenoxycarbonylation of **2** and cyclization of **3**, the only difference is the presence or absence of water. Further, no degradation of **3** occurred under dry conditions even if excess amounts of $NaHCO_3$ existed. From the above results, **3** was prepared from **2** and 4-nitrophenyl chloroformate in the presence of excess amounts of $NaHCO_3$ in dry MeCN, and then only addition of water to the reaction mixture gave **1** (Scheme 2, Table 3).[11] However, in the case of Run 6, the intramolecular cyclization will be retarded by steric hindrance of the *tert*-butyl group, so that water may attack 2-isocyanatocarboxamide (**4f**) to regenerate **2f**, which reacts with **4** to give urea (**5**). The yield of **1f** was improved when 1.0 equimolar amount of triethylamine was used instead of water (Run 7).

Table 3. One-pot preparation of (*S*)-**1** from (*S*)-**2**

Run	R^1	R^2	R^3	Product[a]	Yield/%	*E.e.*/%[b]
1[c]	CH_2Ph	H	H	(*S*)-**1a**	96	>99
2[c]	CH_2Ph	H	Ph	(*S*)-**1b**	94	>99
3[d]	CH_2Ph	H	$(CH_2)_2Ph$	(*S*)-**1c**	96	>99
4[c]	$-(CH_2)_3-$		Ph	(*S*)-**1d**	68[f]	>99
5[c]	CH_2Ph	H	Pr	(*S*)-**1e**	92	>99
6[c]	CH_2Ph	H	*t*-Bu	(*S*)-**1f**	28[g]	>99
7[c]	CH_2Ph	H	*t*-Bu	(*S*)-**1f**	78[h]	>99
8[d]	*i*-Pr	H	Ph	(*S*)-**1g**	96	98
9[d]	CH_2-3-indolyl	H	Pr	(*S*)-**1h**	96	>99
10[e]	CH_2OBu^t	H	$(CH_2)_2Ph$	(*S*)-**1i**	92	99
11[e]	$CH_2CO_2Bu^t$	H	$(CH_2)_3Ph$	(*S*)-**1j**	90	>99

[a]The structures of these compounds were supported by IR, Mass, and ^1H NMR spectra. [b]*E.e.* was determined by HPLC. Conditions: Run 1; column, Chiralpak WH (Daicel Chemical Industries, Ltd.), 1.0 mL/min of 0.25 mmoldm^{-3} $CuSO_4$, detection, 254 nm, other Runs; column, Sumichiral OA-4700 (Sumika Chemical Analysis Service, Ltd.), 1.0 mL/min of hexane:EtOH=9:1, detection, 254 nm. [c]HCl salt. [d]4-Toluenesulfonic acid salt. [e]Free amine. [f]The starting material (**3d**) was recovered in 14% yield. [g]Urea (**5**) was obtained as a main product. [h]Triethylamine (1.0 equiv.) was used instead of water and the reaction mixture was stirred for 12 h after adding Et_3N. Urea (**5**) was obtained in 21% yield.

It has been reported that racemic-**1a** has a melting point of 186 °C[12] and (*S*)-**1a** has a melting point of 181-183 °C[13] or 182 °C.[14] Although the melting point (185-186 °C) of synthesized racemic-**1a** according to the literature was the same as that of the reported one, the melting point of (*S*)-**1a** obtained by our procedure was 171-172 °C, and was apparently different from that of the reported (*S*)-**1a**. Therefore, we undertook a racemization check of synthesized **1** by HPLC. A peak corresponding to the optically active hydantoin was identified by comparison with the standard hydantoin derived from racemic- or (*R*)-amino acid run under identical conditions (Table 3). It was found that the present reaction proceeded without racemization under the reaction conditions.

Similar to degradation of 4-nitrophenyl *N*-methylcarbamate under basic conditions, it is assumed that the present reaction will mainly proceed through the initial formation of **4** by treatment of **3** with $NaHCO_3$ in MeCN-H_2O. Isocyanate (**4**), in turn, gives the corresponding hydantoin (**1**) by its cyclization (elimination-addition process). Since formation of **4** is impossible when **2d** is used as the starting material, the reaction will proceed by an addition-elimination process.

In conclusion, we have developed one-pot preparation of hydantoins from amino acid amide utilizing decomposition of 4-nitrophenyl *N*-substituted carbamate under weakly basic conditions without racemization.

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10 **3a**: mp 132 °C (decomp.); **3b**: mp 136 °C (decomp.); **3c**: mp 127-128 °C (decomp.); **3d**: mp 137-138 °C.
11 One-pot preparation of **1**: to a suspension of amino acid amide (0.3 mmol) and $NaHCO_3$ (0.9 mmol) in dry MeCN (5 mL) was added 4-nitrophenyl chloroformate (0.3 mmol) at room temperature. After being stirred for approximately 3 h, water (3 mL) was added and the reaction mixture was stirred for approximately 3 h. After removal of MeCN under reduced pressure, the organic materials were extracted with EtOAc. The organic layer was washed with 5% K_2CO_3 solution and brine successively, and was dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by preparative TLC on silica-gel and hydantoin **1** was isolated. (*S*)-**1a**: ^1H NMR (300 MHz, DMSO-d_6) δ 2.96 (1H, dd, J = 6.6 and 13.9 Hz), 3.12 (1H, dd, J = 4.4 and 13.9 Hz), 4.23 (1H, dd, J = 4.4 and 6.6 Hz), 7.20-7.30 (5H, m), 7.35 (1H, brs), 10.28 (1H, brs).
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