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Preparation of Resin-Bound Ketimines via Transimination and Its Application in the Synthesis of Hydantoin Libraries

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Abstract : *N*-H Ketimines were prepared from various ketones and ammonia using titanium tetrachloride and were used to form resin-bound ketimines via transimination. They were applied to the solid phase synthesis of hydantoins **1** with four substituent variations using two other building blocks (amino acids and isocyanates). The desired products were obtained with high purity in moderate to good yields in 5 steps.

Imines are highly versatile intermediates in organic synthesis. In solid phase organic synthesis (SPOS), resin-bound aldimines were easily prepared at mild conditions[1] and have been used to prepare a variety of nitrogen heterocycles[2] such as hydantoins,[2a] diketopiperazines,[2b] diketomorpholines,[2b] *N*-mercaptoacyl pyrrolidines,[2c] β-lactams,[2d, 2e] β-sultams,[2f] 4-thiazolidinones,[2g] 2,3-dihydro-4-pyridones,[2h] 4-amino-3,4-dihydro-2-(*1H*)-quinolinones,[2i] etc. In contrast, a general method of preparing resin-bound ketimines has not been reported and they are not commonly used intermediates in SPOS.[3] We could find only a few examples for the preparation of resin-bound ketimines via transimination of *N*-H ketimines as ketone equivalents. Formation of benzophenone imine was used to temporarily increase the acidity of the α-carbon for alkylation in solid phase unnatural peptide synthesis,[4] and in the synthesis of benzodiazepines.[5] However, diaryl variants were mainly prepared presumably because other *N*-H ketimines were generally unstable.[6]

As for the preparation of *N*-H ketimines including aryl alkyl cases and alkyl alkyl cases, indirect routes were reported, such as nucleophilic addition of Grignard reagents to nitriles[7] and deoxygenation of ketoximes.[8] A more intriguing and simpler method is a direct route from parent ketones, but only diaryl variants were prepared using ammonium chloride[9] or titanium tetrachloride[10] as catalysts. By employing modified titanium tetrachloride procedure,[11] we could easily prepare *N*-H ketimines from aryl alkyl ketones and even from a hindered dialkyl ketone.[12] It enabled us to prepare resin-bound ketimines from resin-bound primary amines successfully. To exploit the resin-bound ketimine formation using *N*-H ketimines, we targeted solid phase synthesis of hydantoins **1** with four folds of diversity.

Hydantoin derivatives are attractive targets for drug discovery because of their biological behavior.[13] Since the first report on the solid phase synthesis of hydantoin libraries[5] from two kinds of building blocks (amino acid derivatives and isocyanates), there have been many reports on hydantoins with diverse substituents.[2a, 4e, 14] In the recent examples reported by Kim[14c] and by Matthews,[14d] three folds of diversity was generated by using aldehydes as building block via reductive alkylation.[2b, 15] We followed similar route except for the preparation of secondary amine intermediate **5**.

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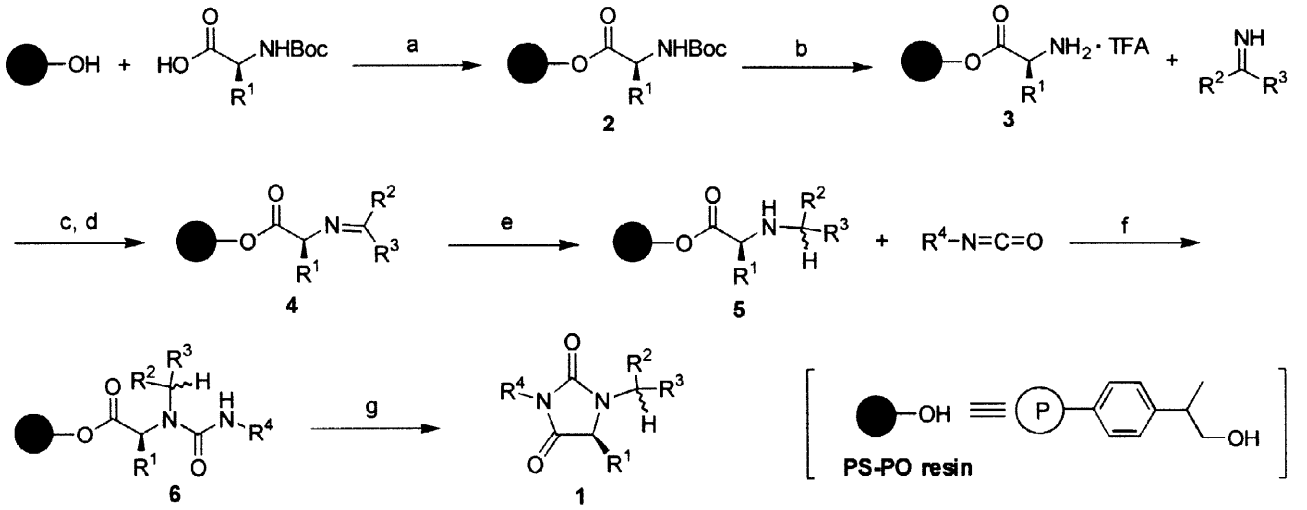

Scheme 1. (a) diisopropylcarbodiimide (DIC), 4-dimethylaminopyridine (DMAP), *N,N*-dimethylformamide (DMF), RT, 18 hrs; (b) 25% trifluoroacetic acid (TFA)/CH_2Cl_2, RT, 1 min and repeated for another 30 min; (c) CH_2Cl_2, RT, overnight, or 1,2-dichloroethane, 50 °C, overnight; (d) Ac_2O, *i*-Pr_2NEt, CH_2Cl_2, RT, 30 min; (e) $NaBH_3CN$, AcOH, *N,N*-dimethylacetamide (DMA); (f) CH_2Cl_2, RT, 1 day, or 3 days; (g) *i*-$PrNH_2$, RT, 1 hr, or 6 hrs

A representative, twenty-member library of hydantoins **1** was constructed using three *tert*-butoxycarbonyl (Boc)-protected amino acids and six *N*-H ketimines and five isocyanates. The general synthetic procedure of hydantoins **1** is outlined in scheme 1 and the results are summarized in Table 1.

Boc-protected amino acids were coupled to our lab. made PS-PO resin[16] to afford **2** (initial loadings were 1.1~1.2 mmol/g starting from 1.5 mmol -OH/g). To provide the secondary amine intermediate **5** from **3**, we performed a 2-step procedure: i.e. (1) Transimination of resin-bound amino acid with *N*-H ketimine; (2) Reduction of the resulting resin-bound ketimine intermediate. For this library, we chose three different types of *N*-H ketimines, aryl alkyl (neutral, electron-deficient, electron-rich, and cyclic), diaryl, and hindered dialkyl, to examine the broad utility of this reaction. After Boc deprotection of **2** and *in-situ* TFA salt formation, **3** was transiminated with 6 equiv. of *N*-H ketimine to give resin-bound ketimine **4**. In the case of using benzophenone imine, a different reaction condition was employed (entries **1e**, **1o**, and **1t**). Then, unreacted primary amine was blocked by acetylation.[17] Resin-bound ketimine **4** was reduced using $NaBH_3CN$ in the presence of AcOH to provide the secondary amine **5**. Conversion to the secondary amine was confirmed by ninhydrin color test.[18]

We compared our 2-step alkylation protocol using *N*-H ketimines as a key feature with the known reductive alkylation procedures using carbonyl compounds. Accordingly, conversion of **3** to **5** (where R^1 = benzyl, R^2 = methyl, and R^3 = phenyl) was performed under the two representative conditions using acetophenone. The remaining two steps (**5** to **6**; where R^4 = Ph, **6** to **1p**) were performed under the same conditions shown in scheme 1. When *N,N*-dimethylacetamide (DMA) was used as a solvent,[14c] we obtained only non-alkylated hydantoin and no desired product was found. When trimethylorthoformate (TMOF) was used,[14d] desired product **1p** was formed as per identification by GC analysis. However, the yield based on the mass of the crude product was much lower (30% vs 91% in our case). More importantly, the purity of **1p** was <30% (compared to 98% in our case), presumably because of the incomplete formation of resin-bound ketimine intermediate.[19]

Treatment of corresponding secondary amine **5** with 10 eqiv. of isocyanate gave the resin-bound urea **6**. Total yields were greatly dependent on the urea formation step (**5** to **6**). In the cases of sterically demanding secondary amines (entries **1n**, **1o**, **1s**, and **1t**) or alkyl isocyanates (entries **1l** - **1m**), which are less reactive than aryl isocyanates, prolonged reaction time (3 days) was required to give moderate to good yields. In the cases of highly hindered secondary amines, low yield was obtained (entry **1t**) and no desired product was obtained

(entry **1n**). Base promoted cyclization/cleavage[14c] using neat *i*-PrNH$_2$ gave the desired hydantoins as diastereomeric mixtures in ratios from 1.1:1 to 5:1.[20,21] Purities were very good (>90%) for all the compounds.

Table 1. Hydantoin Libraries Using Amino Acids, *N*-H Ketimines, and Isocyanates

Entry	R^1	R^2, R^3	R^4	Conditions[a]	Yield(%)[b]	Purity(%)[c]
1a	H	Me, Ph	Ph		92	98
1b	H	Me, 4-ClPh	Ph		98	93
1c	H	Me, 4-(MeO)Ph	Ph		86	98
1d	H		Ph		98	97
1e	H	Ph, Ph	Ph	A	83	98
1f	Me	Me, Ph	Ph		86	98
1g	Me	Me, 4-ClPh	Ph		90	95
1h	Me	Me, 4-(MeO)Ph	Ph		78	95
1i	Me		Ph		98	98
1j	Me		3-ClPh		98	98
1k	Me		2-Cl-5-(CF_3)Ph		95	97
1l	Me		*i*-Pr	B, C	70	98
1m	Me		*n*-Bu	B, C	69	98
1n	Me	*i*-Pr, *i*-Pr	Ph	B	-	-
1o	Me	Ph, Ph	Ph	A, B	61	98
1p	Bz	Me, Ph	Ph		91	98
1q	Bz	Me, 4-ClPh	Ph		74	95
1r	Bz	Me, 4-(MeO)Ph	Ph		94	97
1s	Bz		Ph	B	77	98
1t	Bz	Ph, Ph	Ph	A,B	12	96

[a] Different reaction conditions A: **3** to **4**, solvent (1,2-dichloroethane), 50 ℃; B: **5** to **6**, reaction time (3 days); C: **6** to **1**, cyclization/cleavage time (6 hrs)

[b] Yields are based on the mass of product and are relative to the initial loading.

[c] Purities were checked by GC. All compounds listed above have ^{1}H-NMR data, consistent with the proposed structure.

In summary, preparation of resin-bound ketimines via transimination was investigated by using *N*-H ketimines derived from a broad range of parent ketones. It was applied to the solid phase synthesis of hydantoins **1** affording good results. Applications of resin-bound ketimines to the SPOS of other classes of nitrogen heterocycles are still under investigation and will be reported in a separate paper.

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12. General procedure for the preparation of *N*-H ketimines: Dry CH_2Cl_2 (60mL) was added to liquid ammonia (5mL; 20 eqiv.) in dry ice/acetone bath. 1*M* $TiCl_4/CH_2Cl_2$ (10mL; 1 eqiv.) was added to the solution to form a yellow suspension. After stirring for 30 minutes, ketone (10mmol, 1eqiv.)/CH_2Cl_2 (5mL) was added to the reaction mixture. The bath was removed and the reaction mixture was stirred overnight. Conversion of ketone to ketimine was monitored by GC and the reaction was completed within 1 day except for 2,4-dimethyl-3-pentanone (3 days). The reaction mixture was filtered and washed with small portion of CH_2Cl_2. Combined filtrates were transferred to 100ml volumetric flask, filled with CH_2Cl_2 to 100ml, and stored at –20℃. Purity of *N*-H ketimine solution by GC analysis was above 90%. *N*-H ketimine solutions were used without further purification, except evaporation prior to use to remove excess ammonia.
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19. By-products were non-alkylated hydantoin (15%), unknown (35%), and others (25%). Unknown impurities seemed to be resulted from reaction of primary amine with TMOF, because blank experiment (same experimental procedure, only without acetophenone) showed identical unknown peak on GC chromatogram
20. Diisopropylamine used in ref. 14c did not work in our system. After cyclization, no laborious work up was needed. To remove trace amine salt and colorizing impurities, crude materials were dissolved and filtered through about $1cm^3$ silica gel with ethyl acetate, and evaporated to give products as white solid or oil.
21. Selected ^{1}H-NMR and MS data for compound **1p** (major diastereomer = A, minor diastereomer = B)
^{1}H-NMR(500 MHz, $CDCl_3$): δ(ppm) 6.95-7.49(m, 42 H, Ar*H*, *A*+*B*), 5.43(q, *J*=7.3Hz, 1H, B), 4.96(q, *J*=7.3Hz, 1.8H, A), 4.32(dd, *J*=4.7, 4.1Hz, 1.8H, A), 4.11(dd, *J*=4.9, 3.9Hz, 1H, B), 3.25(dd, *J*=14.4, 3.9Hz, 1H, B), 3.17(dd, *J*=14.4, 4.9Hz, 1H, B), 3.13(dd, *J*=14.4, 4.1Hz, 1.8H, A), 2.94(dd, *J*=14.4, 4.7Hz, 1.8H, A), 1.86(d, *J*=7.3Hz, 3H, B), 1.84(d, *J*=7.3Hz, 5.4H, A).
LRMS (EI, *m/z*): 370 (M^+, 11), 279 (9), 105 (100).