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Efficient Synthesis of Highly Functionalized Cyclic Aminimides

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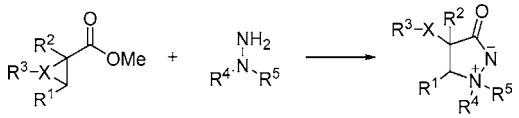
ABSTRACT

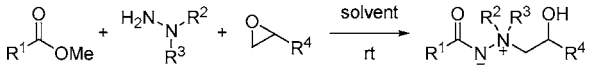


Simple condensation reactions of various α,β-epoxy or α,β-aziridinyl methyl esters with 1,1-dialkyl hydrazines provided cyclic aminimides (1,1-dialkyl-3-oxopyrazolidines) with a heteroatom substituent at the 4-position in good yields. The reaction proceeds smoothly, without any coreagent, providing the product as an easily isolable precipitate. The reaction is expected to be a good candidate for combinatorial synthesis of a highly functionalized five-membered ring scaffold. The scope and limitations of this reaction were investigated by varying the substituents R^1–R^5.

As the combinatorial approach continues to gain prevalence in drug discovery, the demand for efficient procedures for generating a scaffold with high functionality is increasing.[1] Among the various scaffold-generating strategies, multicomponent reactions have drawn a lot of attention because they quickly provide relatively complex and biologically interesting core structures with high degrees of functionalization under mild conditions.[2] In this respect, the three-component reaction of an ester, a 1,1-dialkyl hydrazine, and an epoxide (Scheme 1)[3] is undoubtedly an attractive one for molecular library construction because the reaction has up to five variable sites: R^1 (ester), R^2 and R^3 (hydrazine), and R^4 and R^5 (epoxide). Most of all, the simple reaction conditions (just mixing the substrates in a protic solvent or polar aprotic solvent such as DMSO without any coreagent) and purification procedure (simple filtration) make this reaction a powerful tool for building combinatorial libraries. The importance of variable substituents and simple conditions for combinatorial synthesis has been demonstrated by Rutenber and co-workers.[4] They noticed that hydroxyaminimide **1** resembles the peptide hydrolysis transition state. Accordingly, they constructed a peptide isostere library using this three-component reaction (Scheme 1) in search of effective HIV-1 protease inhibitors. Additionally, Ringe and co-worker demonstrated that a peptidomimetic aminimide could be an effective inhibitor of porcine pancreatic elastase (PPE) by showing the X-ray structure of the PPE−inhibitor complex.[5]

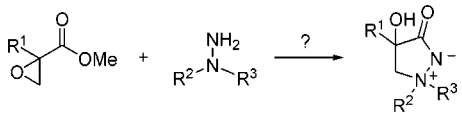
To expand the utility of this powerful reaction, we envisioned integrating the ester and epoxide functionalities into one molecule to provide a cyclic aminimide as shown in Scheme 2. Although linking two components into one molecule may

Scheme 1 Three-Component Reaction of an Ester, a 1,1-Dialkyl Hydrazine, and an Epoxide



1

Scheme 2. Cyclic Aminimide Formation with an Epoxy Ester and a 1,1-Dialkyl Hydrazine



2 **3** **4**

(1) (a) Ivachtchenko, A. V.; Il'yin, A. P.; Kobak, V. V.; Zolotarev, D. A.; Boksha, L. V.; Trifilenkov, A. S.; Ugoleva, D. M. *J. Comb. Chem.* **2002**, 419. (b) Wunberg, T.; Kallus, C.; Opatz, T.; Henke, S.; Schmidt, W.; Kunz, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 2503.
(2) Weber, L. *Curr. Med. Chem.* **2002**, *9*, 2085.
(3) Slagel, R. C. *J. Org. Chem.* **1968**, *33*, 1374.

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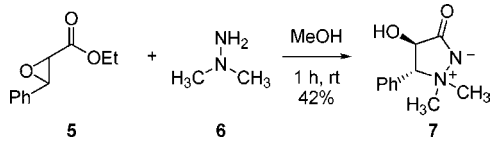
reduce the number of variable sites, this drawback is compensated by the potential advantages of the newly generated cyclic skeleton, which may be an interesting pharmacophore.

A review of the literature revealed the work of Sucrow and co-workers (Scheme 3).[6] In the late 1970s, the Sucrow

Scheme 3 Reaction of 3-Phenylglycidyl Methyl Ester (**5**) and 1,1-Dimethyl Hydrazine (**6**) Described in Ref 6

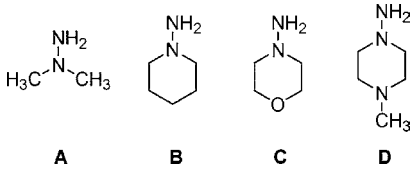


5 **6** **7**

group reported that *trans*-1,1-dimethyl-4-hydroxy-5-phenyl-pyrazolidin-3-one (**7**) was obtained in 42% yield from the reaction of *trans*-3-phenylglycidic acid ethyl ester (**5**) and 1,1-dimethyl hydrazine (**6**) in methanol at room temperature. The corresponding *cis*-glycidic ester afforded the *cis*-cyclic aminimide under the same conditions. To the best of our knowledge, these are the only examples of this type of reaction in the literature.

In this article, we wish to report the scope and limitations of this reaction for cyclic aminimide library synthesis by screening the utility of combining various epoxy or aziridinyl esters and 1,1-dialkyl hydrazines.

Initially, we prepared epoxy esters **8**−**11** following literature procedures[7] and reacted these esters with commercially available 1,1-dialkyl hydrazines **A**−**D** (Figure 1).



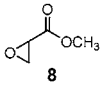
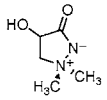
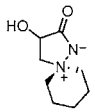
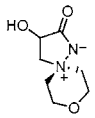
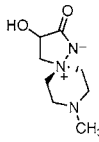
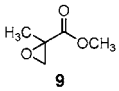
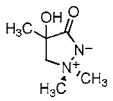
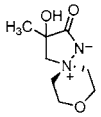
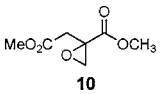
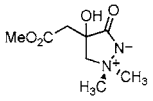
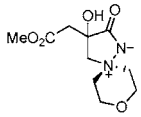
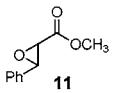
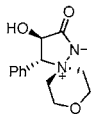
A **B** **C** **D**

Figure 1. 1,1-Dialkyl hydrazines used in this study.

The structures and yields of the products are provided in Table 1. All the reactions proceeded smoothly in a protic solvent (*i*PrOH), and the products precipitated during the reaction. In most cases, simple filtration of the reaction mixture yielded the desired cyclic aminimides in high purity (>95%) as judged by ^{1}H NMR and elemental analyses (EA).

When the reactions were carried out in more polar protic solvents such as methanol or ethanol, the yields were lower,

Table 1. Reactions of Epoxy Esters with Various 1,1-Dialkyl Hydrazines

entry	epoxy ester	hydrazine	product	reaction time[a]	yield[b]
1	 **8**	**A**	 **12**	3 h	95%
2		**B**	 **13**	5 h	71%
3		**C**	 **14**	5 h	49%
4		**D**	 **15**	4 h	45%
5	 **9**	**A**	 **16**	6 h	67%
6		**C**	 **17**	4 h	53%
7	 **10**	**A**	 **18**	5 h	62%
8		**C**	 **19**	12 h	35%
9	 **11**	**C**	 **20**	6 h	75%

[a] All reactions were carried out in ^{i}PrOH at room temperature. [b] Isolated yields.

probably due to the higher solubility of the products in these solvents compared to their solubility in *i*-PrOH.

The reaction of glycidic acid methyl ester **8** with dimethyl hydrazine (**A**) yielded the corresponding cyclic aminimide **12** in high yield (95%). When ester **8** was reacted with cyclic hydrazines such as **B**−**D**, the cyclic aminimides were obtained in somewhat lower yields. This trend was valid for other 2- or 3-substituted glycidic acid methyl esters such as **9**−**11**. Although alkyl substitution at the ester 2-position yielded the desired cyclic aminimides in reasonable yields as shown in entries 5−8, alkyl substitution at 3-position did not provide any product. Only β-aryl-substituted ester **11** yielded the condensed product as shown in entry 9.

All of the resulting cyclic aminimides were water-soluble white solids with high melting points (>200 °C).[8] Each

(4) Rutenber, E. E.; McPhee, F.; Kaplan, A. P.; Gallion, S. L.; Hogan, J. C., Jr.; Craik, C. S.; Stroud, R. M. *Bioorg. Med. Chem.* **1996**, *4*, 1545.
(5) Peisach, E.; Casebier, D.; Gallion, S. L.; Furth, P.; Petsko, G. A.; Hogan, J. C., Jr.; Ringe, D. *Science* **1995**, *269*, 66.
(6) Sucrow, W.; Slopianka, M.; Vetter, H-J. *Chem. Ber.* **1978**, *111*, 791.
(7) (a) Nemes, A.; Czibula, L.; Visky, G.; Farkas, M.; Kredl, J. *Heterocycles* **1991**, *32*, 2329. (b) Glabe, A. R.; Sturgeon, K. L.; Ghizzoni, S. B.; Musker, W.; Takahashi, J. N. *J. Org. Chem.* **1996**, *61*, 7212.

showed a characteristic aminimide absorption at 1570∼1600 cm^{-1} in their IR spectra.[3] Formation of the cyclic aminimide skeleton was also confirmed by X-ray crystallographic analysis of the spirocyclic aminimide **14** (Figure 2).[9]

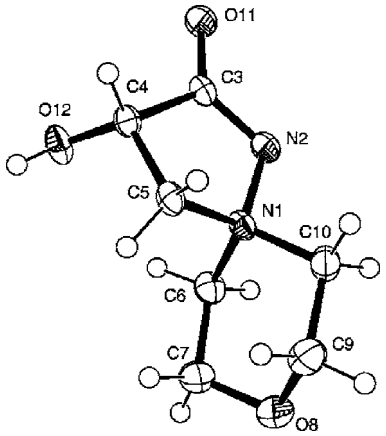
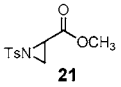
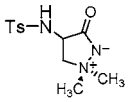
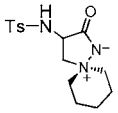
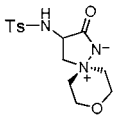
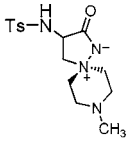
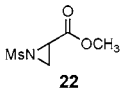
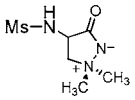
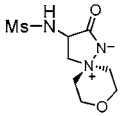
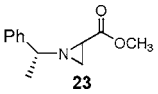


Figure 2. Single-crystal X-ray structure of compound **14**.

To expand the scope of this reaction, we next investigated the analogous reactions with aziridinyl methyl esters **21**−**23** (Table 2). In contrast to the epoxy ester series, aziridinyl esters exhibited more sluggish reactivity and required harsher conditions. At room temperature, the reactions were rather slow. As a result, the reactions were carried out in *i*-PrOH under reflux conditions. When the substituent on the aziridinyl nitrogen is an electron-withdrawing group such as *p*-toluenesulfonyl (Ts) or methanesulfonyl group (Ms), the reaction proceeds smoothly. In these cases, the desired products could be isolated as a white precipitate in reasonably high yields (74−83%). However, when the substituent is a simple alkyl group such as a phenethyl group (entry 7 in Table 2) or a benzyl group, no desired product is observed even under reflux conditions. Several attempts to promote the reactions using a protic acid (TsOH) or Lewis acids [Ti(O*i*Pr)$_4$, Ce(OTf)$_4$, InCl$_3$] failed to provide the desired results. Similar to the reactions of epoxy esters, extra substitution at the β-position of the aziridinyl esters also inhibited the reaction.

In summary, we have investigated the condensation reactions of epoxy esters with various 1,1-dialkyl hydrazines. Additionally, we have found that the scope of the reaction can be extended to the use of aziridinyl methyl esters. These reactions provide highly functionalized cyclic aminimides. The reactions proceeded smoothly in *i*PrOH, yielding the cyclic aminimides as precipitates in good yields. No purification procedures were required other than filtration and washing. Although the reactions of β-substituted derivatives were limited to aryl substitution, we expect that this reaction might be useful in generating pharmaceutically interesting scaffolds. We are currently investigating the bioactivity of these compounds, and the results will be reported in due course.

Table 2. Reactions of Aziridinyl Esters with Various 1,1-Dialkyl Hydrazines

entry	aziridinyl ester	hydrazine	product	reaction time[a]	yield[b]
1	 **21**	**A**	 **24**	5 h	74%
2		**B**	 **25**	6 h	80%
3		**C**	 **26**	5 h	77%
4		**D**	 **27**	5 h	83%
5	 **22**	**A**	 **28**	3 h	82%
6		**B**	 **29**	6 h	77%
7	 **23**	**A**	no reaction		

[a] All reactions were carried out in [i]PrOH at 80 °C. [b] Isolated yields.

Acknowledgment. This work was supported by Grant R14-2002-045-01002-0 from the Advanced Basic Research Laboratory (ABRL) Program and Center for Bioactive Molecular Hybrid (CBMH) of the Korea Science & Engineering Foundation. We thank Mr. Sangwoo Park and Professor M. K. Choi for X-ray crystallographic analysis of compound **14** and Dr. Michael Haukaas for his editorial contributions to the manuscript.

Supporting Information Available: Synthetic procedures and characterization data for all new compounds (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL051270V

(8) Melting points and IR spectral data of the individual compounds are listed in Supporting Information.

(9) X-ray data for compound **14** are available in Supporting Information.