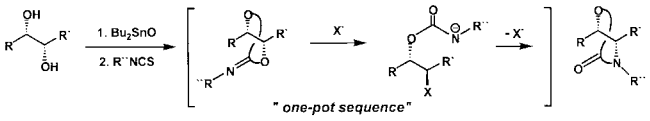
The Cyclic Iminocarbonate Rearrangement: The Scope and Limitations of the *N*-Substituents

Gae Y. Cho, Ji Y. Choi, and Soo Y. Ko*

Department of Chemistry and Division of Molecular Life Sciences, Ewha Womans University, Seoul 120-750, Korea
Received October 15, 2001

Keywords : Cyclic iminocarbonate rearrangement, Amino alcohols, Isothiocyanates.

The cyclic iminocarbonate rearrangement (CIR) provides a means to convert *syn*-diols to *syn*-amino alcohol functionality.[1] This one-pot process actually consists of a series of reactions, including conversion of diol substrates to cyclic iminocarbonates; a nucleophilic ring-opening of the five-membered cyclic intermediates by halides; and finally a nucleophilic ring-closure with the expulsion of the halides (Scheme 1). The double nucleophilic displacements, which take place in a domino fashion, result in a conversion of cyclic iminocarbonates to oxazolidin-2-ones (hence the "rearrangement") wherein the configurations of both carbinol carbons are retained.



Scheme 1

The required cyclic iminocarbonates are conveniently prepared by first activating the diols in the form of the *O*-stannylene ketals, which are then reacted with isothiocyanates.[2] The original protocol of the CIR utilized benzoyl isothiocyanate, a well-considered choice for the ease of the rearrangement itself as well as the subsequently required deprotections to free amino alcohols. In additions, the presence of the *N*-benzoyl substituent was taken advantage of in an atom-economic synthesis of the C-13 side chain of Paclitaxel.[3]

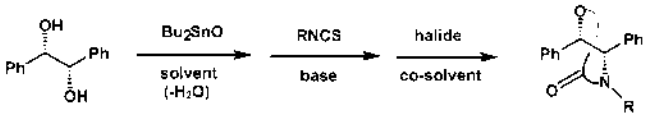
With proper choices of reagents, on the other hand, our CIR process may provide a ready access to *N*-substituted amino alcohols. While primary amino alcohols are recognized as an important functional group for their biological activity as well as for their use as chiral auxiliaries and ligands.[4] *N*-substituted amino alcohols have potential to be as much useful. A series of isothiocyanates were therefore screened in order to determine the scope and limitations of their use in the CIR process.

Stilbene diol (**1**) was selected as the diol substrate. It was first converted to the corresponding *O*-stannylene ketal (with a Dean-Stark removal of water), which was then treated with various isothiocyanates in the presence of base. The resulting cyclic iminocarbonates were observed on TLC, but in most cases not stable enough to be chromatographed on a silica column. The rearrangements therefore were prompted without isolating the intermediates by adding appropriate halide nucleophiles. The results were summarized in the Table.

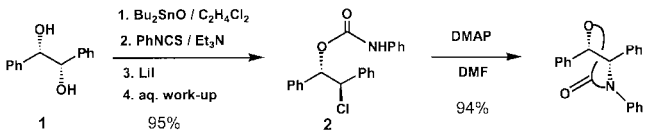
When one considers the course of the rearrangement, i.e., the double displacements (Scheme 1), electron-withdrawing groups on the nitrogen of the cyclic iminocarbonates are expected to facilitate the process.[5] Indeed, employing the original protocol (isothiocyanate with Et_3N; LiI; reflux in dichloroethane) that had been developed for the rearrangement of *N*-benzoyl-substituted cyclic iminocarbonate (entry 1), the reactions with tosyl[6] and ethoxycarbonyl isothiocyanates proceeded readily to produce the corresponding *N*-tosyl- and *N*-ethoxycarbonyloxazolidin-2-ones, respectively (entries 2 and 3).

Substitution of *N*-aryl groups became possible only after some modifications on the reaction conditions as the reaction with phenyl isothiocyanate employing the original protocol took a markedly different course (Scheme 2). When the diol substrate was treated with Bu_2SnO in dichloroethane, then with PhNCS in the presence of Et_3N as usual, the required cyclic imnocarbonate was formed satisfactorily, as judged by TLC and NMR.[7] Upon the addition of LiI, a ring-opening took place not by I^- but by Cl^-.[8] The chloride ion was

Table 1.



entry	RNCS	solvent	base	halide	co-solvent	yield
1	BzNCS	$C_2H_4Cl_2$	Et_3N	LiI	–	73%
2	TsNCS	$C_2H_4Cl_2$	Et_3N	LiI	–	84%
3	EtO_2CNCS	$C_2H_4Cl_2$	Et_3N	LiI	–	89%
4	PhNCS	toluene	Et_3N	LiI	DMF	88%
5	*p*-NO_2-C_6H_4NCS	toluene	Et_3N	LiI	DMF	92%
6	*p*-MeO-C_6H_4NCS	toluene	Et_3N	LiI	DMF	80%
7	EtNCS	toluene	DABCO	LiI	–	46%
8	BnNCS	toluene	DABCO	MgI_2	–	52%



Scheme 2

apparently generated from the only chlorine source present in the reaction mixture: the solvent, dichloroethane. The chloride-opened product, 1,2-diphenyl-1-anilinylcarbonyloxy-2-chloroethane (**2**), refused to proceed with the second displacement *in situ*, but remained unchanged upon prolonged heating (95%). It was isolated and made to undergo the desired ring-closure to the *N*-phenyloxazolidin-2-one only after treating it with base in a separate step (94%). As phenyl group is less electron-withdrawing than sulfonyl or carbonyl group, we speculate that the less reactive cyclic *N*-phenyliminocarbonate needs more nucleophilic Cl^- for the ring-opening step and the ring-opened product, **2**, does not undergo the ring-closure as Cl^- is not so effective a leaving group as I^-.

The one-pot operation was achieved with phenyl isothiocyanate by adopting two modifications on the reaction conditions. When we replaced dichloroethane by more inert and higher-boiling toluene as solvent, and compensated for the decreased polarity of the reaction medium by adding DMF as co-solvent for the double displacement step, the yield of the desired *N*-phenyloxazolidin-2-one was improved to a level comparable to those with carbonyl- or sulfonyl-substituted isothiocyanates (88%, entry 4). Under these conditions, the electron-withdrawing *p*-nitro-substituted phenyl isothiocyanate yielded the desired oxazolidinone in a higher 92% yield (entry 5). The reaction with *p*-methoxyphenyl isothiocyanate was slow, but the desired *N*-*p*-methoxyphenyloxazolidin-2-one was obtained in 80% yield after a prolonged reaction time (entry 6).

The *N*-alkyl-substituted cases initially posed problems as both the cyclic iminocarbonate formation and the subsequent rearrangement steps were sluggish when the reactions were attempted with ethyl and benzyl isothiocyanates. Our efforts for the optimization of the reaction conditions included screening various bases for the cyclic iminocarbonate formation step as well as various halide nucleophiles for the rearrangement step. In the event, use of more nucleophilic base, DABCO, proved efficacious for the cyclic iminocarbonate formation step. Thus, the *O*-stannylene ketal prepared in toluene under reflux was treated with ethyl isothiocyanate in the presence of DABCO. The rearrangement was prompted by addition of LiI to produce the *N*-ethyloxazolidin-2-one in 46% yield (entry 7). Use of DMF co-solvent was detrimental in this case. Under similar conditions and using benzyl isothiocyanate, the *N*-benzyl-substituted oxazolidin-2-one was obtained in 32%. Use of MgI_2 in the rearrangement[3] improved the yield to 52% (entry 8). Obviously, *N*-alkyl groups on the cyclic iminocarbonate weren't strongly electron-withdrawing enough to bring about the double displacements readily, as reflected in the low yields of the *N*-alkyloxazolidin-2-ones even under optimized reaction conditions.

In conclusion, the cyclic iminocarbonate rearrangement can be effected with various *N*-substituents, the electronic nature of which influences the outcomes of the process. With *N*-sulfonyl and *N*-carbonyl groups, the rearrangements proceed readily, while *N*-aryl substitution requires some modifications of the reaction conditions (toluene, Bu_2SnO: ArNCS and Et_3N: LiI and DMF; one-pot process) in order to produce high yields of the *N*-aryloxazolidin-2-ones. *N*-Alkyl-substituted oxazolidin-2-ones can be prepared only in modest yields *via* the cyclic iminocarbonate rearrangement when specifically optimized reaction conditions are employed (toluene, Bu_2SnO: RNCS and DABCO: LiI or MgI_2; one-pot process).

General procedure for the *N*-carbonyl and *N*-sulfonyl substituents. Diol substrate was dissolved in dichloroethane and Bu_2SnO (1.1 eq.) was added. The mixture was heated to reflux for 4 hrs with a concomitant removal of water (Dean-Stark trap). *N*-Carbonyl or -sulfonyl isothiocyanate (1.4 eq.) and triethylamine (1.2 eq.) were added and the mixture was heated for 2 hrs. LiI (1.2 eq.) was added and the entire mixture was heated to reflux for 12 hrs. Aqueous work-up was followed by chromatographic purification to yield the desired product.

General procedure for the *N*-aryl substituents. Diol substrate was dissolved in toluene and Bu_2SnO (1.1 eq.) was added. The mixture was heated to reflux for 4 hrs with a concomitant removal of water (Dean-Stark trap). *N*-Aryl isothiocyanate (2 eq.) and triethylamine (1.2 eq.) were added and the mixture was heated for 48 hrs. The mixture was diluted with DMF (equal volume to toluene) and LiI (1.2 eq.) was added. The entire mixture was heated to reflux for 15 hrs. Concentration was followed by chromatographic purification to yield the desired *N*-aryl-substituted oxazolidin-2-one.

General procedure for the *N*-alkyl substituents. The Sn-ketalization was performed in toluene as described above. *N*-Alkyl isothiocyanate (1.4 eq.) and DABCO (1.1 eq.) were added and the mixture was heated for 7 days. LiI (1.2 eq.) was added and the entire mixture was heated to reflux for 3 days. Concentration was followed by chromatographic purification to yield the desired *N*-alkyl-substituted oxazolidin-2-one.

Acknowledgment. This work was supported by the KRF (2000-015-DP0271). G.Y.C. is grateful to the Brain Korea 21 project for a graduate fellowship.

References and Notes

1. Cho, G. Y.; Ko, S. Y. *J. Org. Chem.* **1999**, *64*, 8745.
2. (a) Yano, K.; Baba, A.; Matsuda, H. *Chem. Ber.* **1991**, *124*, 1881. (b) Baba, A.; Seki, K.; Matsuda, H. *J. Org. Chem.* **1991**, *56*, 2684. (c) Baba, A.; Seki, K.; Matsuda, H. *J. Heterocyclic Chem.* **1990**, *27*, 1925.
3. Cho, G. Y.; An, K. M.; Ko, S. Y. *Bull. Korean Chem. Soc.* **2001**, *22*, 432.
4. (a) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835. (b) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517. (c) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *25*, 117. (d) Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichimica Acta* **1994**, *27*, 3.
5. (a) Barton, D. H. R.; Motherwell, W. *J. Nouv. Chim.* **1978**, *2*, 301. (b) Barton, D. H. R.; Motherwell, W. *J. C. S. Perkin Trans I* **1980**, 1124.
6. Barton, D. H. R.; Fontana, G.; Yun, Y. *Tetrahedron* **1996**, *52*, 2705.
7. The *N*-aryl-substituted cyclic iminocarbonates are generally stable enough to be isolated by silica column chromatography.
8. It was confirmed by the mass spectroscopy of compound **2**.