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Reaction of Azetidines with Chloroformates

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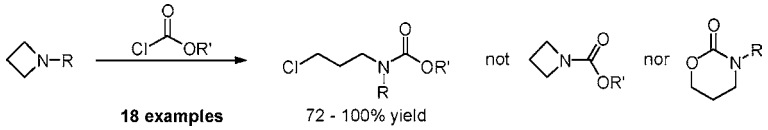
ABSTRACT

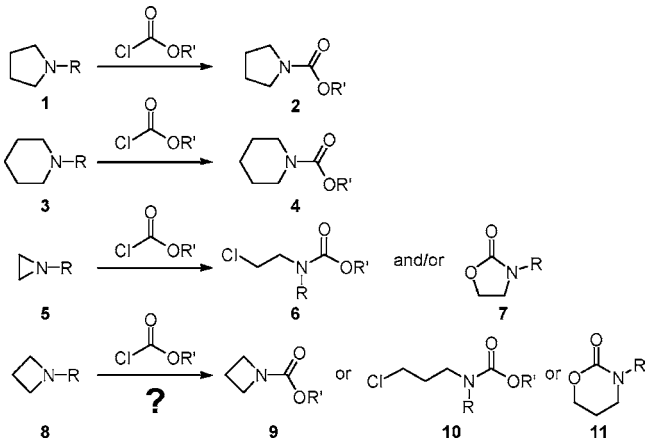


The reaction of an azetidine with a chloroformate can give either the dealkylated heterocycle or the ring-opened product (γ-chloroamine), which can further cyclize to the oxazinanone. A general study of this underrated reaction was conducted and revealed that azetidines can undergo smooth nucleophilic ring-opening reactions to highly functionalized γ-chloroamines in the presence of a variety of alkyl chloroformates under mild reaction conditions. Yields are usually good, and parameters governing this reaction were evaluated.

The reaction of tertiary amines with chloroformates, a variant of the von Braun reaction[1] developed in the 1970s by Olofson, has become a powerful tool in organic synthesis.[2] In most cases, this procedure is especially effective for selective N-demethylation or N-debenzylation reactions, and many chloroformates have been reported to effect these dealkylations in high yields and mild reaction conditions.[3]

The generality of this selective dealkylation reaction has been demonstrated over the years for the N-dealkylation of five-membered (**1**), six-membered (**3**), or larger rings yielding the products resulting from a selective exocyclic dealkylation of general structures **2** and **4** (Scheme 1). The vast number of applications of these procedures on complex substrates clearly demonstrates the broad scope of this mild dealkylation reaction.

Scheme 1. Reaction of Cyclic Tertiary Amines and Chloroformates



Apart from isolated reports, the reactivity of the smaller aziridines **5** with chloroformates has been studied only recently. The behavior of this three-membered ring heterocycle was found to dramatically differ from that of the five-membered and larger rings since β-chloroamines **6** and/or oxazolidinones **7** are produced and debenzylation is not even a competitive pathway anymore (Scheme 1).[4,5]

Surprisingly, careful examination of literature showed that only a few isolated publications have reported on the reaction

(1) Hageman, H. A. *Org. React.* **1953**, *7*, 198.
(2) (a) Kapnang, H.; Charles, G. *Tetrahedron Lett.* **1983**, *24*, 3233. (b) Cooley, J. H., Evain, E. J. *Synthesis* **1989**, 1.
(3) Ethyl chloroformate: (a) Flynn, E. H.; Murphy, H. W.; McMahon, R. E. *J. Am. Chem. Soc.* **1955**, *77*, 3104. (b) Campbell, J. A. *J. Org. Chem.* **1957**, *22*, 1259. Aryl chloroformates: (c) Hobson, J. D.; McCluskey, J. G. *J. Chem. Soc. C* **1967**, 2015. (d) Pfaffli, P.; Hauth, H. *Helv. Chim. Acta* **1973**, *56*, 347. Vinylchloroformate: (e) Olofson, R. A.; Rodney, C. Schnur, R. C.; Bunes, L.; Pepe, J. P. *Tetrahedron Lett.* **1977**, *18*, 1567. Chloroethyl chloroformate: (f) Olofson, R. A.; Martz, J. T.; Senet, J.-P.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081. 2,2,2-Trichloroethyl chloroformate: (g) Montzka, T. A.; Matiskella, J. D.; Partyka, R. A. *Tetrahedron Lett.* **1974**, *15*, 1325. β-Trimethylsilylethyl chloroformate: (h) Campbell, A. L.; Pilipauskas, D. R.; Khanna, I. K.; Rhodes, R. A. *Tetrahedron Lett.* **1987**, *28*, 2331. Propargyl chloroformate: (i) Bhat, R. G.; Ghosh, Y.; Chandrasekaran, S. *Tetrahedron Lett.* **2004**, *45*, 7983.

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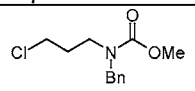
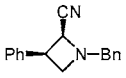
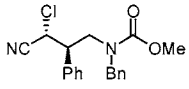
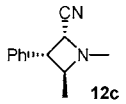
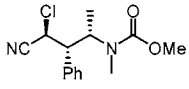
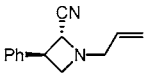
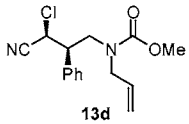
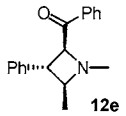
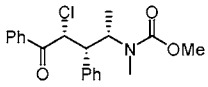
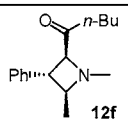
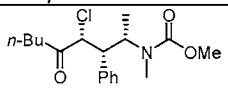
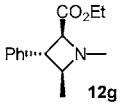
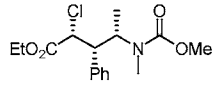
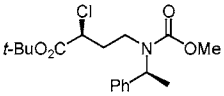
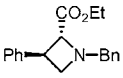
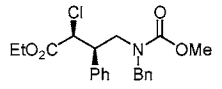
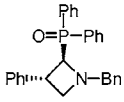
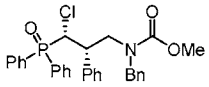
Table 1. Ring Opening of Azetidines with Methylchloroformate

entry	azetidine [a]	γ-chloroamine [a,b]	yield [c,d]
1	 **12a**	 **13a**	100%
2	 **12b**	 **13b**	81%
3	 **12c**	 **13c**	90%
4	 **12d**	 **13d**	90%
5	 **12e**	 **13e**	87%
6	 **12f**	 **13f**	80%
7	 **12g**	 **13g**	86%
8	 **12h**	 **13h**	78%
9	 **12i**	 **13i**	82%
10	 **12j**	 **13j**	94%

[a] ee ≥95% in all cases. See ref 9b and 10 for the synthesis of starting azetidines. [b] Position of the chlorine atom on the carbon chain was assigned by ^{1}H NMR analysis when unambiguous or by analysis of the corresponding reduced products after reaction with tributyltin hydride and AIBN. See Supporting Information for details. [c] de ≥95% in all cases. [d] Yield of pure, isolated products.

of azetidines with chloroformates: while 3-oxo-[6] or 3-alkenyl-*N*-benzhydryl-azetidine[7] gave the dealkylated azetidines, the formation of ring-opened product as a byproduct was reported twice.[8] In our continuing efforts to expand the usefulness of azetidine chemistry,[9] as well as to provide a predicting tool, we undertook a systematic study of this reaction. We therefore disclose in this publication studies establishing that azetidines **8** can be induced to undergo smooth nucleophilic ring-opening reactions to γ-chloroamines **10**, without competitive formation of dealkylated azetidine **9** or oxazinanone **11** (Scheme 1).

As a test reaction, *N*-benzylazetidine **12a** was reacted with methylchloroformate in dichloromethane at room temperature (Table 1, entry 1). After 12 h, the only product that could be detected in the crude reaction mixture resulted form the ring-opening reaction yielding to the *N*-protected γ-chloroamine **13a**, which could be further isolated in quantitative yield.

Pleased by this quite promising result and unexpected selectivity, our attention was turned to the generality of the process, and the reactivity of a range of structurally diverse enantiopure azetidines, previously synthesized in our group,[10] toward methylchloroformate was studied. Results are shown in Table 1 and clearly show that polysubstituted enantiopure γ-chloroamines **13** are obtained in good yields without competitive N-dealkylation or formation of oxazinanone. Interestingly, the ring-opening process itself proved to be highly regioselective (opening of the intermediate *N*-acyl azetidinium chloride at the more electrophilic position).

More importantly, the reaction is completely stereospecific (a S_N2 process was observed for the ring opening of aziridines[4,11] and is supported by calculations described at the end of the manuscript), and no epimerization at the reacting centers is observed (de ≥95% in all cases). Finally, a wide range of functional groups are compatible with the mild reaction conditions.

To further understand the parameters driving this reaction, we next focused on the influence of the relative stereochem-

(4) (a) Sim, T. B.; Kang, S. H.; Lee, K. S.; Lee, W. K.; Ha, H.-J. *J. Org. Chem.* **2003**, *68*, 104. (b) Park, C. H.; Kim, M. S.; Sim, T. B.; Pyun, D. K.; Lee, C. H.; Choi, D.; Lee, W. K.; Chang, J.-W.; Ha, H.-J. *J. Org. Chem.* **2003**, *68*, 43. (c) Kim, Y.; Ha, H.-J.; Yun, H.; Lee, B. K.; Lee, W. K. *Tetrahedron* **2006**, *62*, 8844.

(5) Ennis, D. S.; Ince, J.; Rahman, S.; Shipman, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2047.

(6) Nitta, Y.; Yamaguchi, Y.; Tanaka, T. *Heterocycles* **1986**, *24*, 25.

(7) (a) Vuilhorgne, M.; Commercon, A.; Mignani, S. *Chem. Lett.* **1999**, 605. (b) Tonder, J. E.; Hansen, J. B.; Begtrup, M.; Petterson, I.; Rimvall, K.; Christensen, B.; Ehrbar, U.; Olesen, P. H. *J. Med. Chem.* **1999**, *42*, 4970.

(8) (a) Baumann, H.; Duthaler, R. O. *Helv. Chim. Acta* **1988**, *71*, 1035. (b) Barrett, A. G. M.; Dozzo, P.; White, A. J. P.; Williams, D. J. *Tetrahedron* **2002**, *58*, 7303.

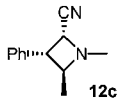
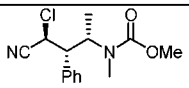
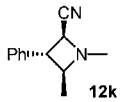
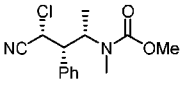
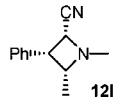
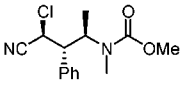
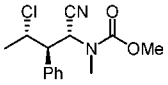
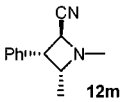
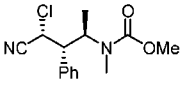
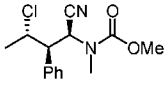
(9) (a) Couty, F.; Evano, G.; Prim, D. *Mini-Rev. Org. Chem.* **2004**, *1*, 133. (b) Couty, F.; Evano, G.; Vargas-Sanchez, M.; Bouzas, G. *J. Org. Chem.* **2005**, *70*, 9028. (c) Vargas-Sanchez, M.; Couty, F.; Evano, G.; Prim, D.; Marrot, J. *Org. Lett.* **2005**, *6*, 5861. (d) Bräuner-Osborne, H.; Bunch, L. Chopin, N., Couty, F.; Evano, G.; Jensen, A. A.; Kusk, M.; Nielsen, B.; Rabasso, N. *Org. Biomol. Chem.* **2005**, 3926−3936. (e) Sivaprakasam, M.; Couty, F.; Evano, G.; Srinivas, B.; Sridhar, R.; Rama Rao, K. *Synlett* **2006**, 781. (f) Couty, F.; David, O.; Durrat, F.; Evano, G.; Lakhdar, S.; Marrot, J.; Vargas-Sanchez, M. *Eur. J. Org. Chem.* **2006**, 3479.

(10) (a) 2-Cyano-azetidines: Agami, C.; Couty, F.; Evano, G. *Tetrahedron: Asymmetry* **2002**, *13*, 297. (b) 2-Acyl-azetidines: Couty, F. Prim, D. *Tetrahedron: Asymmetry* **2002**, *13*, 2619. (c) 2-Carboxy-azetidines: Couty, F.; Durrat, F.; Prim, D. *Tetrahedron Lett.* **2003**, *44*, 5209. Also see ref 9b. (d) 2-Phosphinoyl-azetidines: Rabasso, N. Ph.D. dissertation, Université Pierre et Marie Curie, France, 2003.

(11) Kim, Y.; Ha, H. J.; Han, K.; Ko, S. W.; Yun, H.; Yoon, H. J.; Kim, M. S.; Lee, W. K. *Tetrahedron Lett.* **2005**, *46*, 4407.

istry of the azetidine by reacting four diastereoisomers of a tetrasubstituted azetidine under the same reaction conditions (Table 2). As evidenced by the results obtained from these experiments, the relative configuration of the starting material clearly has a crucial influence on the regioselectivity of the ring-opening process, since a reverse regioselectivity was even observed starting from the *trans*,*cis* diastereoisomer **12m**.

Table 2. Stereochemistry Influences the Regioselectivity.

Azetidine [a]	γ-chloroamine [a,b,c,d] (C_2 opening)	γ-chloroamine [a,b,c,d] (C_4 opening)	C_2/C_4 opening ratio [e]
 **12c**	 **13c** (90%)	–	> 95/5
 **12k**	 **13k** (72%)	–	> 95/5
 **12l**	 **13l** (56%)	 **13l'** (34%)	65/35
 **12m**	 **13m** (37%)	 **13m'** (60%)	39/61

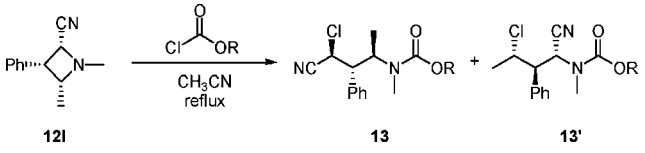
[a] ee ≥95% in all cases. See ref 10a for the synthesis of starting azetidines. [b] Position of the chlorine atom on the carbon chain was assigned by ^{1}H NMR analysis when unambiguous or by analysis of the corresponding reduced products after reaction with tributyltin hydride and AIBN. See Supporting Information for details. [c] Yield of pure, isolated products. [d] de ≥95% in all cases. [e] Determined by ^{1}H NMR analysis of crude reaction mixture.

At this point of our study, it seemed crucial to also evaluate and compare the reactivity of various chloroformates. To this end, azetidine **12l**, which gave a mixture of regioisomers when reacted with methyl chloroformate, was chosen as model substrate and was reacted with a series of chloroformates in refluxing acetonitrile[12] Results obtained from this comparative study are summarized in Table 3. Surprisingly, the nature of the chloroformate has virtually no influence; both yields and regioisomeric ratios are highly comparable. Here again, no products resulting from N-dealkylation could be detected, which clearly demonstrates the wide scope of this reaction.

In order to shed some light on the difference in reactivity of azetidines versus larger *N*-heterocycles, a comparison experimental/theoretical study of the reaction of *N*-benzylazetidine **12a** and *N*-benzylpyrrolidine **15** toward methylchloroformate was performed.[13] Therefore, **12a** and **15** were first reacted with methylchloroformate in dichloromethane

(12) Reactions were in most cases too sluggish and did not go to completion with this particular all-*cis* azetidine when run in DCM. Therefore, they were all run in refluxing acetonitrile to have comparable results.

Table 3. Survey of Chloroformates

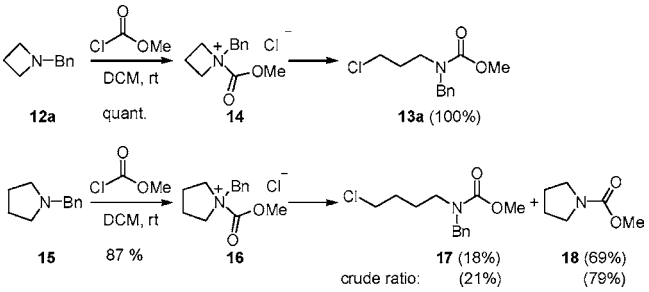


R	**13** (C_2 opening)[a]	**13′** (C_4 opening)[a]
Me	56% (**13l**)	34% (**13l′**)
Et	54% (**13n**)	36% (**13n′**)
*i*Pr	50% (**13o**)	30% (**13o′**)
allyl	51% (**13p**)	33% (**13p′**)
Bn	52% (**13q**)	30% (**13q′**)
vinyl	64% (**13r**)	30% (**13r′**)

[a] ee ≥95% in all cases. See ref 10a for the synthesis of **12l**. Position of the chlorine atom on the carbon chain was assigned by ^{1}H NMR analysis when unambiguous or by analysis of the corresponding reduced products after reaction with tributyltin hydride and AIBN. See Supporting Information for details. Yield of pure, isolated products; de ≥95% in all cases.

at room temperature. Whereas **12a** quantitatively gave the product resulting from a ring-opening reaction (**13a**) with complete regioselectivity, a mixture of ring-opened product **17** (minor product) and debenzylated pyrrolidine **18** (major product) were obtained when starting from the five-membered ring **18** (Scheme 2).

Scheme 2. Compared Reactivity of *N*-Benzylazetidine versus *N*-Benzylpyrrolidine



Having these experimental results in hand, we next focused on a theoretical approach relying on density functional theory (DFT)[14] at the B3LYP[15]/6-31G*[16] level, computed using Gaussian 03; energy profiles obtained from these calculations are shown in Figure 1. Starting from azetidinium ion **14** and approaching the two reactants leads first to a molecular complex **MC1**[17] in which the azetidine ring is almost undistorted. From this complex **MC1**, there are two possible

(13) For a theoretical approach of the formation of oxazolidinones from aziridines, see: Testa, L.; Akssira, M.; Zaballos-García, E.; Arroyo, P.; Domingo, L. R.; Sepúlveda-Arques, J. *Tetrahedron* **2003**, *59*, 677.

(14) (a) Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989. (b) Ziegler, T. *Chem. Rev.* **1991**, *91*, 651.

(15) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(16) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab initio Molecular Orbital Theory*; Wiley: New York, 1986.

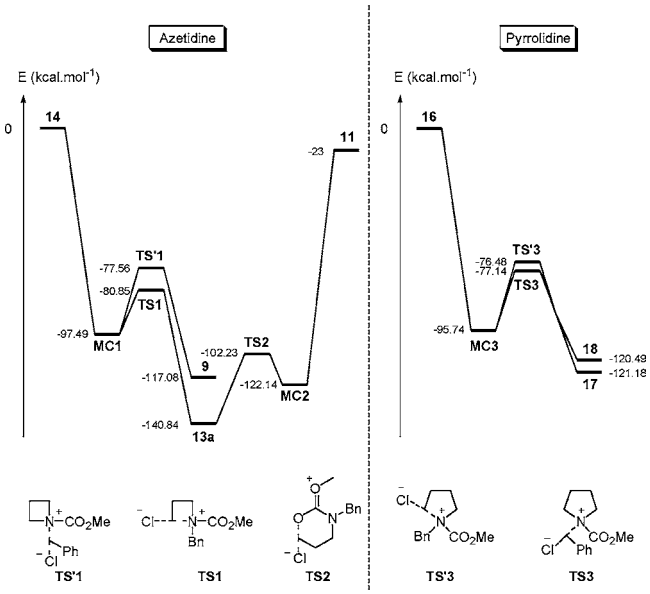


Figure 1. Energy profiles for the stationary points corresponding to the reaction of *N*-benzylazetidine and *N*-benzylpyrrolidine with methylchloroformate.

pathways yielding products **9** (debenzylated azetidine via **TS′1**) and **13a** (ring-opened product via **TS1**). As shown by the energy profile (Figure 1), the difference in activation energy between the two pathways is equal to 3.28 kcal mol^{-1}, which is in good agreement with the observed exclusive formation of the ring-opened product **13a** and can be attributed to a release of the ring strain in the corresponding transition state **TS1**. Interestingly, the formation of oxazinanone **11** from γ-chloroamine **13a** would require an activation energy of 38.6 kcal mol^{-1}, therefore explaining why this product could not be detected in the crude reaction mixture.

A different reactivity was found for the reaction of *N*-benzylpyrrolidinium ion **16** since computationally the energy difference between the two pathways (ring opening vs debenzylation) is, in this case, much lower. If the debenzylation pathway yielding to **18** (via **TS3**) becomes the more favorable one, there is now only 0.66 kcal mol^{-1} difference in energies, which should correspond to a 75/25 ratio of **18**/**17** (Figure 1). This results perfectly fits the experimental 79/21 ratio obtained in the case of *N*-benzylpyrrolidine **15** (Scheme 5), and the dramatic difference between the reactivity of azetidine **12a** and pyrrolidine **15** toward methylchloroformate can most certainly be attributed to the huge difference in strain energies of these heterocycles (6 kcal mol^{-1} for pyrrolidine compared with 25 kcal mol^{-1} for azetidine).[18]

We have shown that the reaction of azetidines with chloroformates gives highly functionalized γ-chloroamines in high yields and selectivities under mild reaction conditions. The process is very flexible with regard to the substituents on the azetidine ring, and most common chloroformates can be used. An interesting and unexpected feature disclosed in this study is the unusual reactivity of azetidines compared to larger ring systems: ring strain definitely seems to play a crucial role in the reaction and allows for high levels of regioselectivities. Further use of both ring-opening protocol and highly functionalized building blocks obtained will be reported in due time.

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Supporting Information Available: Protocol used for the structure determination of regioisomers; spectroscopic data and experimental procedures for all new compounds; copies of ^{1}H and ^{13}C NMR spectra; Cartesian coordinates and Gaussian output files for transition and ground states. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The gas-phase S_N2 reaction is known to proceed via a molecular complex. See for examples (a) Parthiban, S.; de Oliveira, G.; Martin, J. M. L. *J. Phys. Chem. A* **2001**, *105*, 895; (b) Bouyacoub, A.; Jean, Y.; Volatron, F. *J. Mol. Struct.* **1996**, *371*, 51 and references cited therein.

(18) Bach, R. D.; Dmitrenko, O. *J. Org. Chem.* **2002**, *67*, 3884.