Tetrahedron Letters 56 (2015) 6625–6628

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Reaction of *N*-alkyl azetidines with triphosgene

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ARTICLE INFO

Article history:
Received 9 September 2015
Revised 7 October 2015
Accepted 9 October 2015
Available online 19 October 2015

Keywords:
Azetidines
Urea
Ring cleavage
Triphosgene

ABSTRACT

N-Alkyl azetidines react with triphosgene (BTC) following two possible pathways: *N*-alkyl ring scission or ring cleavage, to give cyclic or acyclic *N*-carbamoyl chlorides. Predominance of one pathway over the other is governed by the nature of the substituents on the azetidine ring and on the nitrogen atom as well as by the relative stereochemistry of the ring substituents, and is examined in detail. Some azetidines were identified for their privileged reaction pathway, leading to new functionalized building blocks that were further elaborated into five- or six-membered urea or into azetidinic urea.

Azetidines are clearly gaining attention within the past decade as privileged scaffolds for the development of new pharmaceuticals.[1] This can be ascribed both from the growing knowledge allowing to prepare these heterocycles, especially in enantiomerically pure form,[2] but also from patent strategy. In these strained heterocycles, the nature of the protecting group on the nitrogen atom is of utmost importance, and influences to a large extent their reactivity which is governed by their strain: *N*-alkyl azetidines being generally less prone to ring opening than their *N*-acyl or *N*-sulfonyl analogues under acidic conditions.[3] Apart from pure synthetic considerations, the inter-conversion between *N*-alkyl and *N*-acyl group in azetidines is an important issue which lacks generality[4] and is rendered difficult because of the ring strain. In this context, alkyl chloroformates, which are popular reagents to promote such reaction in tertiary amines, react mainly with *N*-alkyl azetidines through a ring opening[5] (Scheme 1, path A). We report herein the use of BTC (bis-trichloromethylcarbonate, triphosgene), a safe substitute for phosgene,[6] which reacts with *N*-alkyl azetidines following two possible pathways: *N*-alkyl cleavage (Scheme 1, path B), or ring cleavage (path A) depending on the substrate. The resulting products can then be further elaborated into different ureas, thus illustrating the chemical diversity that can be reached with these heterocycles.[7]

In a preliminary series, we selected azetidines **1**–**4** fitted with a *N*-Bn protecting group, as substrates for reaction with BTC, since it is known that such substituent is cleaved preferably upon reaction with alkylchloroformates. On the other hand, the presence of the cyano group allows for further functionalization.[2g] Results are depicted in Scheme 2.

Reaction occurs readily in dichloromethane at room temperature with mono and disubstituted **1** and **2** to give exclusively ring-opened compounds with moderate regioselectivity favouring C-2 cleavage. When trisubstituted azetidines **3** and **4** are involved, no reaction occurs, even with protracted reaction time.

We next selected *N*-benzhydryl azetidines **9**, **12** and **16** as substrates, aiming at favoring cleavage of the *N*-substituent. Thus, commercially available **9** readily reacted with BTC[8] to give a mixture of carbamoyl chloride **10**[9] and opened product **11**, in a 7:3 ratio, based on the examination of the crude reaction mixture by NMR. On the other hand, *N*-benzhydryl 2-cyano azetidine **12** and trisubstituted ephedrine-derived *N*-benzhydrylazetidine **16** (9:1 epimeric mixture at C-2), prepared following Scheme 3,[10] were found to be completely inert towards BTC, similarly to **3** and **4**, thus illustrating the high sensitivity of this reaction towards steric crowding around the nitrogen atom.

In the series of *N*-benzylic substrates, diastereoisomeric azetidines **17** and **20**, readily prepared from (*S*)-phenylethylamine,[4d] and fitted with a substituted benzyl group were also reacted with BTC, to provide interesting chiral functionalized azetidinic carbamoyl chlorides **18** and *ent*-**18**, together with minor amounts of opened products **19** and **21**. Compounds **18** and *ent*-**18** could be conveniently isolated by flash chromatography in 54% and 58% yields, respectively (Scheme 4).

Finally, we also tested the reaction of BTC on encumbered trisubstituted azetidines **22** and **23** fitted with a smaller *N*-methyl substituent, compared to a *N*-Bn (**3**–**4**) or a *N*-benzhydryl (**16**). In this case, reaction with BTC was effective, but we noticed an important influence of the relative configuration at C-2/C-3 on

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http://dx.doi.org/10.1016/j.tetlet.2015.10.036
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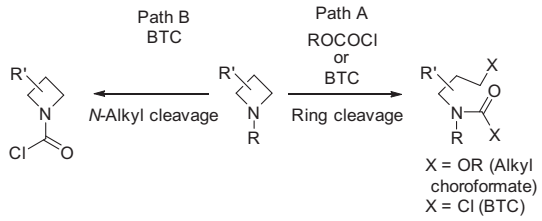
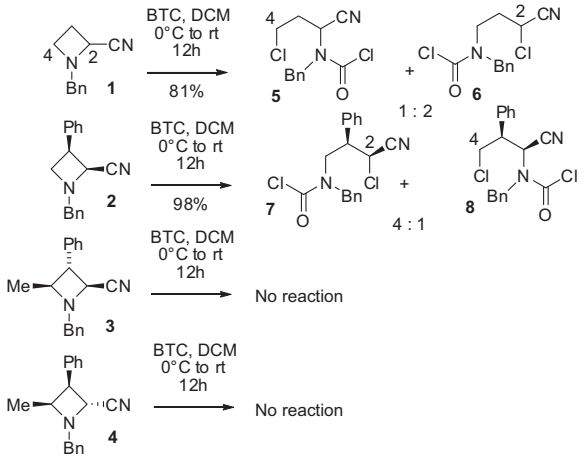
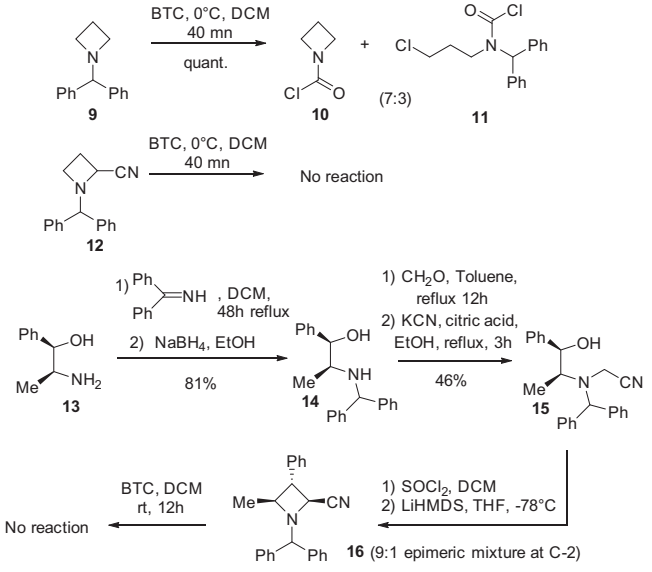


Scheme 1. BTC (triphosgene) reacts with *N*-alkyl azetidines following two pathways, depending on the substituents on the azetidine ring.

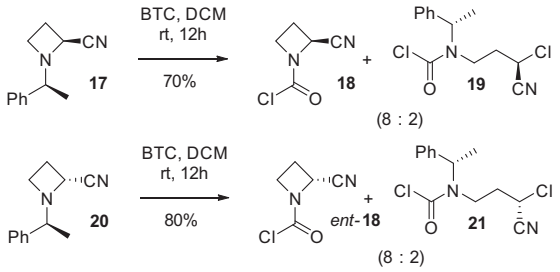


Scheme 2. BTC (triphosgene) reacts with *N*-benzyl azetidines exclusively through ring-opening.



Scheme 3. Reaction of *N*-benzhydryl azetidines with BTC (triphosgene).

the yield and selectivity: while 2,3-*cis* compound **22** reacted rapidly to give good yield of isolated ring-opened regioisomer **24**, reaction with 2,3-*trans* isomer **23** was more sluggish and gave mixtures from which, compounds **25**–**27** were isolated (Scheme 5). It should be mentioned that in this case, BTC behaves differently from simple chloroformates, since the reaction of **23** with MeOCOCl occurs uneventfully to give high yield of one regioisomer resulting from C-2 cleavage.[5b]

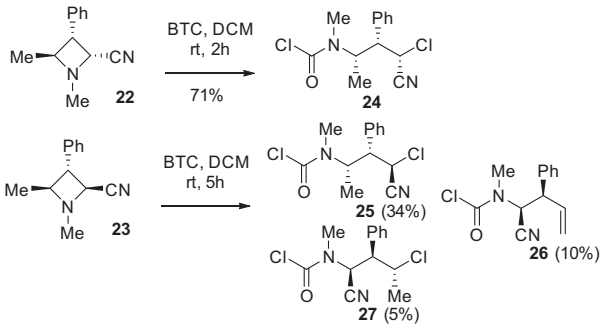


Scheme 4. In **17** and **20**, *N*-phenylethyl substituent is preferably cleaved by BTC (triphosgene).

Rationalization of all the above results is not straightforward. Particularly striking is the difference of reactivity of **1**, compared to **17** and **20**, the former leading exclusively to ring opening while the latter favoring N-dealkylation. As matter of fact, an overview of this reaction includes two steps that should be considered independently: (i) N-acylation of the azetidine with phosgene (or triphosgene initially), which is mainly governed by steric hindrance around the nitrogen atom and explain the inertia of encumbered substrates. In this first step, each of the four conformers and invertomers of the azetidine are able to react and their relative population is not known. Then (ii) attack of the chloride anion at the carbon atoms adjacent to the *N*-acylated atom, leading either to ring opening or dealkylation. This last step was shown previously to follow a S_N2 mechanism[2e,g] and is extremely sensitive to steric hindrance. Subtle parameters can drastically influence the ease of this step, and the privileged cleavage of the *N*-(1-phenylethyl) group in **17** and **20** compared to the *N*-Bn group in **1** might reflect a better stabilization of the positive charge partially developed in the transition state brought by the methyl substituent.

Next, in order to implement possible uses of the produced compounds, we investigated their transformation into tetrahydropyrimidin-2-ones and imidazolidin-2-ones, which are skeletons existing in many synthetic biologically active compounds.[11] To this end, a mixture of carbamoyl chlorides **5** and **6** was reacted with benzylamine to afford the corresponding mixture of regioisomeric ureas **28** and **29**, which were subjected to ring closure by intramolecular N-alkylation of the urea nitrogen upon treatment with NaH in THF. Pyrimidin-2-one **30** was thus obtained in 54% overall yield. When this two-step operation was conducted with isolated carbamoyl chloride **7**, an unexpected issue was observed, because in this case, partial β-elimination of the chloride occurred in **31**, yielding imidazolidin-2-one **33** as the major compound, resulting from conjugate addition on the intermediate cyano alkene **32**, together with small amounts of tetrahydropyrimidin-2-one **34**, produced by nucleophilic substitution in **31**. Formation of the five-membered ring was however suppressed when an additional methyl group was introduced on the carbon backbone. Thus, when carbamoyl chloride **24** was used as the substrate, tetrahydropyrimidinones **36** and **37** were produced in a good overall yields as a (6:4) epimeric mixture (Scheme 6). Relative configuration in these epimers was unambiguously determined by ^{1}H NMR: assuming a fixed configuration for the methyl substituent at C-6, isomers were minimized by AM1 calculations, which showed that 4,5-*cis* isomer displayed a dihedral angle of 45° for H-4/H-5, while 4,5-*trans* isomer showed a value of 180°. The large (10.6 Hz) observed ^3J H4–H5 value for H-5 in major isomer **36** and the small one (3 Hz) in minor **37** reflects an epimerization at C-4 in basic medium.

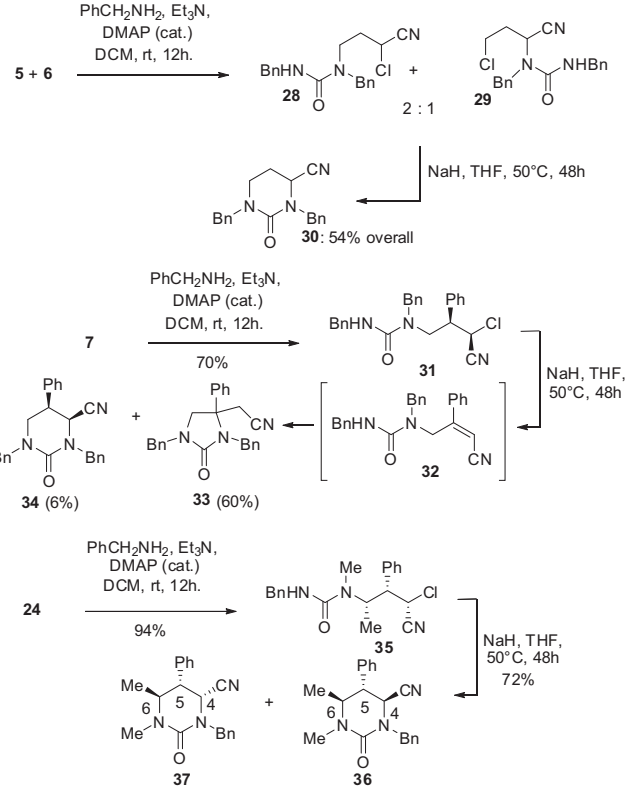
Next was studied the functionalization of chlorocarbamoyl azetidines **10**, **18** and *ent*-**18**. To this end, crude mixture of **10** and **11** resulting from the reaction of **9** with BTC (Scheme 3) was directly



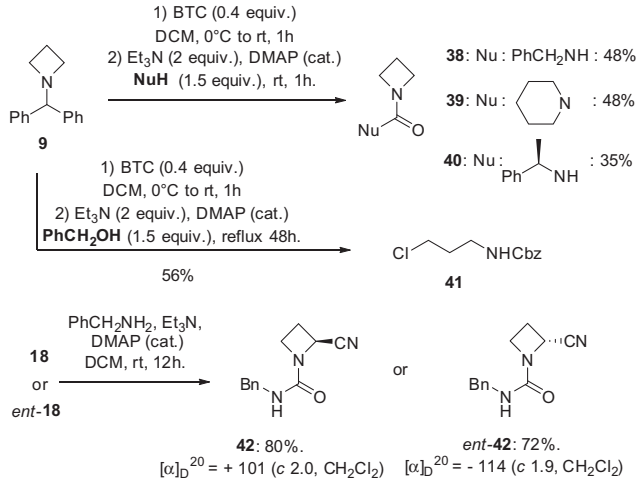
Scheme 5. Effect of relative configuration in the azetidine ring for reaction with BTC.

reacted with amines in order to prepare the corresponding azetidinic urea. Indeed, **10** was difficult to purify on a small scale and it was more convenient to delay the purification step. Reaction occurred without ring cleavage and gave azetidinic urea **38**–**40** that could be conveniently purified at this stage by flash chromatography and were isolated in fair yields, considering the 7:3 selectivity of the first step. However, aniline was unreactive following these conditions, and benzyl alcohol required protracted reaction time and heating, leading essentially to ring cleavage to give **41**. Alternatively, **18** and *ent*-**18** gave **42** and *ent*-**42** in good yields (Scheme 7).

In conclusion, we have demonstrated herein that triphosgene can induce selective cleavages in *N*-alkyl azetidines, providing useful building blocks for chemical diversity targeting cyclic ureas or azetidinic ureas.



Scheme 6. Transformation of ring opened products into cyclic urea.



Scheme 7. Reactions of chlorocarbamoyl azetidines.

Acknowledgments

University of Versailles St-Quentin-en-Yvelines and CNRS are acknowledged for financial support.

Supplementary data

Supplementary data (typical experimental procedures and characterization data for cyclic ureas **30**, **33**, **36**, **37** and azetidines **18**, **38**, **42**. Copies of ^{1}H and ^{13}C NMR data for these compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.10.036.

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