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Heterocyclization of *gem*-dichlorocyclopropanes: "Fine tuning" of reactivity towards nitronium triflate

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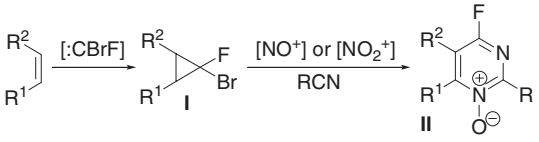
ABSTRACT

The heterocyclization of *gem*-dichlorocyclopropanes upon treatment with nitronium triflate in organic nitriles was studied and the influence of the medium on the reaction pathway was shown. While in anhydrous solvent 5-chloroisoxazole was the only product, the admixture with water promoted a three-component heterocyclization affording 4-chloropyrimidine *N*-oxides. This phenomenon was rationalized using DFT calculations.

Introduction

The pyrimidine and quinazoline rings are frequently encountered structural units in the design of pharmaceuticals with a wide range of activities, including anticonvulsant, antibacterial, antifungal, antiviral and anticancer properties.[1] 1,3-Diazaheterocycles, which contain halogens at the *o*- or *p*-positions in relation to the nitrogen atoms and, therefore, can be readily modified *via* S_NAr or cross-coupling processes, represent common synthetic intermediates in the construction of heterocyclic compound libraries for bioactivity screening.[2] However, approaches to halogenopyrimidines are mostly restricted to halogenation of the pyrimidine ring, while the direct synthesis *via* heterocyclization is represented by significantly fewer examples[3]

Previously, we reported the heterocyclization of *gem*-bromofluorocyclopropanes **I** to give 4-fluoropyrimidine *N*-oxides **II** upon treatment with nitrosating or nitrating reagents in the presence of organic nitriles (Scheme 1), and preparative approaches towards various pyrimidine derivatives based on this reaction.[4]



Scheme 1. Synthesis of pyrimidine *N*-oxide derivatives *via* the three-component heterocyclization of bromofluorocyclopropanes.

This reactivity was restricted to 1-bromo-1-fluoro substituted cyclopropanes; the reaction of *gem*-dichlorocyclopropanes with reagents such as $NOBF_4$ or $NOCl{\cdot}SO_3$ in acetonitrile did not afford products from introduction of the nitrile moiety into the molecule, instead leading to 5-chloroisoxazoles.[5] Therefore, it remained a challenging task to engage *gem*-dichlorocyclopropanes into the three-component heterocyclization with nitrating reagents. This approach to 4-halogenopyrimidine oxides would be very attractive since it utilises the most available and least reactive type of dihalogenocyclopropanes and adheres to the principle of atom economy by preventing the waste of a bromine atom on the two-step synthetic pathway from an alkene to a 4-halogenopyrimidine *N*-oxide **II** (Scheme 1).

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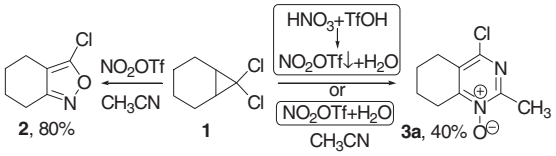
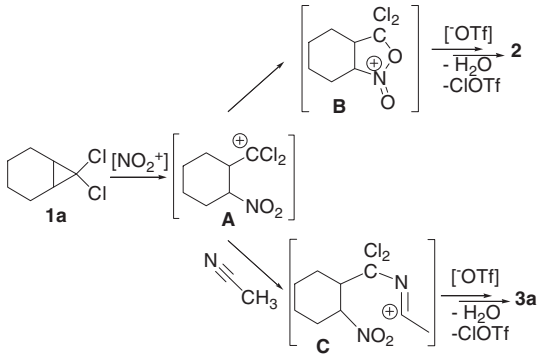


Scheme 2. Reaction pathways for the heterocyclization of dichlorobicycloheptane **1** upon treatment with nitrating agents.



Scheme 3. Two probable pathways for the transformation of carbocation **A**.

Results and discussion

For this purpose, model dichlorocyclopropane **1a** was investigated by treatment with nitronium triflate in acetonitrile; this was previously found to be the most efficient system for the heterocyclization of bromofluorocyclopropanes into pyrimidine derivatives.[4b] The reaction of **1a** with NO_2OTf either at r.t. or reflux exclusively afforded 5-chloroisoxazole **2** in good yield (Scheme 2), reproducing the literature data[5] for various [NO^+] and [NO_2^+] sources.

However, the *in situ* generation of nitronium triflate from fuming nitric and triflic acids altered the reaction pathway towards the formation of 4-chloropyrimidine *N*-oxide **3a**, representing the first example of the targeted reactivity of *gem*-dichlorocyclopropanes (Scheme 2).[6,7] The same result was obtained, when an equimolar quantity of water was added to the mixture of cyclopropane **1a** and NO_2OTf in acetonitrile.

Previously,[4a,c] we proposed a mechanism for the three-component heterocyclization, including the formation of carbocation **A** and a Ritter-like reaction of **A** with a molecule of acetonitrile as the key stages.[8] Taking this into account, we carried out DFT computations for the two competing processes: 1) the cyclization of carbocation **A** to give intermediate **B**, affording isoxazole **2** *via* a series of eliminations, and 2) the nucleophilic addition of acetonitrile to carbocation **A** leading to **C**, the precursor of pyrimidine *N*-oxide **3a** (Scheme 3).

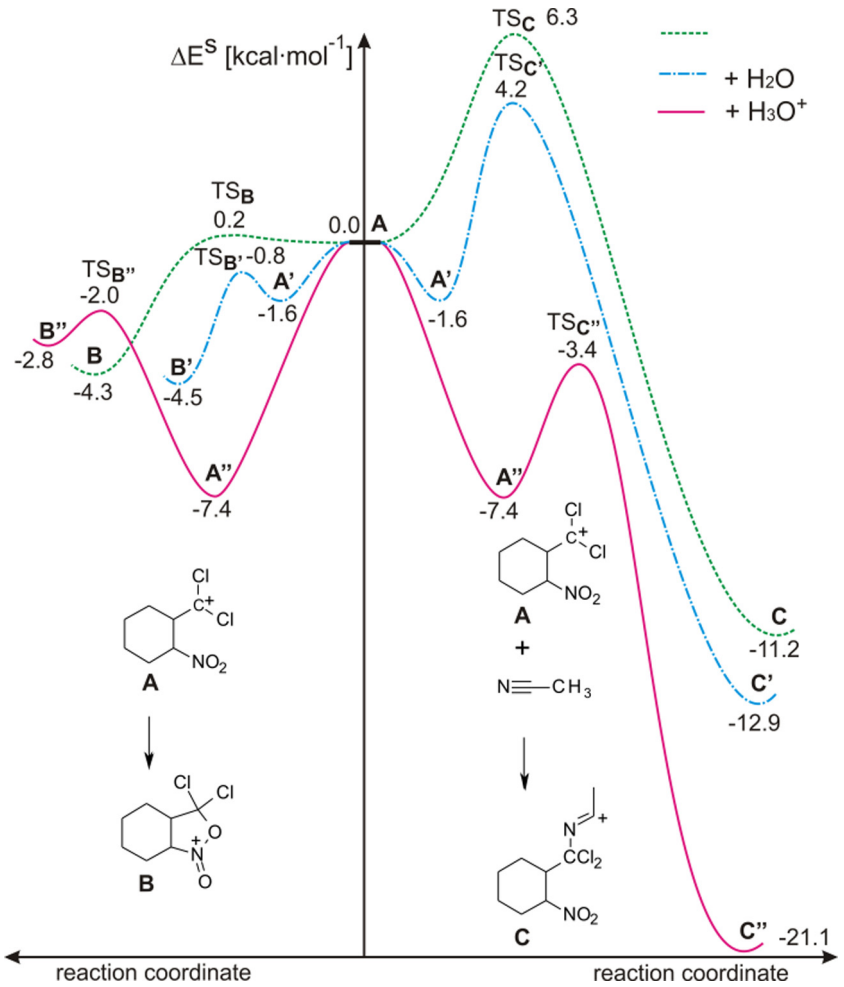
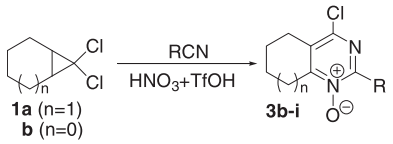


Fig. 1. Minimum energy pathways for the cyclization of carbocation **A** (left part) and acetonitrile addition (right part) in acetonitrile. The single mark ′ denotes a complex with H_2O. The double mark ″ denotes a complex with H_3O^+.

Table 1
Preparation of pyrimidine *N*-oxides **3b–i**.



1a (n=1)
b (n=0)

3b-i

N	R	R^1	R^2	Yield **3** (%)[a]
3b	Et	-$(CH_2)_4$-		21
3c	*i*-Pr	-$(CH_2)_4$-		7
3d	*t*-Bu	-$(CH_2)_4$-		45
3e	*cy*-Pr	-$(CH_2)_4$-		15
3f	*cy*-Hex	-$(CH_2)_4$-		52
3g	-$(CH_2)_3$Cl	-$(CH_2)_4$-		47
3h	Me	-$(CH_2)_3$-		49
3i	*t*-Bu	-$(CH_2)_3$-		26

[a] Isolated yield. Reagents and conditions: **1** (1.0 mmol), HNO_3 (2.0 mmol), TfOH (2.0 mmol), RCN (1 mL), 7 d, r.t.

All DFT calculations were performed using the B3LYP exchange-correlation functional,[9] together with the standard 6-311+g(d,p) basis set,[10] using the Gaussian 09 package.[11] Minimum energy paths were calculated by IRC method.[12]

According to the DFT calculations (Fig. 1, also see ESI), the participation of a hydroxonium ion in the reaction is crucial for determining the reaction pathway. In the absence of a proton the preferable reaction pathway is an intramolecular cyclization of carbocations **A** or **A′**, requiring to overcome quite low energy barriers (0.2 or 0.8 kcal·mol^{-1}, respectively). The resulting product of these transformations is an isoxazole. On the contrary, the coordination of the hydroxonium ion with the nitro-group oxygen of carbocation **A** changes the reaction pathway. As a result, the cyclization of complex **A″** requires an activation energy 1.0 kcal·mol^{-1} higher than the addition of acetonitrile. Additionally, cyclization product **B″**, generated under these conditions, has low kinetic stability and is destabilized relative to the starting complex **A″**. Therefore, it undergoes rapid reverse transformation with the barrier as low as 0.8 kcal·mol^{-1}. At the same time nucleophilic addition of acetonitrile to complex **A″** gives the very stable adduct **C″** (stabilization energy is 21.1 kcal·mol^{-1}), which undergoes further transformations affording pyrimidine *N*-oxide **3a**.

To demonstrate the generality of this process we varied the dichlorocyclopropane and nitrile components and obtained a series of previously unknown 4-chloropyrimidine *N*-oxides **3b–i** (Table 1). It should be noted, that dichlorocyclopropane **1a** proved to be less reactive than the analogous bromofluorocyclopropane[4c] and the reaction required either high temperature or extended time, and was accompanied by decomposition of the organic material. Another side-process observed in the reaction was the formation of minor quantities of isoxazole **2** and transformation of the nitrile into the corresponding diamide derivatives under acidic conditions.[13] The product of this reaction with isobutyronitrile, diisobutyramide, was isolated and its structure determined by single-crystal X-ray analysis (ESI).[14]

Due to the aforementioned processes, the yields of heterocycles **3a-g** are lower (Table 1), when compared to the analogous 4-fluoropyrimidine derivatives.[4] Nevertheless, taking into account the exceptional preparative availability of *gem*-dichlorocyclopropanes, this approach towards 4-halogenopyrimidine oxides may represent a reasonable alternative to previously described synthetic approaches. Thus, heterocyclization of cyclopropane **1b** affords heterocycles **3h**,**i**, containing the previously not described dihydro-5*H*-cyclopenta[*d*]pyrimidine motif, in satisfactory yields.[15]

In conclusion, we have succeeded in shifting the reaction pathway for the reaction of *gem*-dichlorocyclopropanes with nitrating reagents in organic nitriles using a medium effect. This represents the first example of a three-component heterocyclization of this class of compounds, which provides a novel approach towards 4-chloropyrimidine *N*-oxides employing readily available *gem*-dichlorocyclopropanes.

Acknowledgments

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A. Supplementary data

Supplementary data (experimental procedures, characterization data for all obtained compounds, X-ray data for diisobutyramide, computational details and copies of NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.06.047.

References

1. (a) Cheng GC. In: Ellis GP, West GB, editors. *Progress in Medicinal Chemistry*, Vol. 6. Amsterdam: Elsevier B.V.; 1969:67–134;
(b) Cheng GC, Roth B. In: Ellis GP, West GB, editors. *Progress in Medicinal Chemistry*, Vol. 7. Amsterdam: Elsevier B.V.; 1970:285–341;
(c) Cheng GC, Roth B. In: Ellis GP, West GB, editors. *Progress in Medicinal Chemistry*, Vol. 8. Amsterdam: Elsevier B.V.; 1971:61–117;
(d) Rewcastle GW, Roth B. In: Katritzky AR, Ramsden CA, Scriven EFV, Taylor RJK, editors. *Comprehensive Heterocyclic Chemistry III*, Vol. 8. Oxford: Elsevier Ltd.; 2008:120–272;
(e) Singh K, Kaur T. *Med Chem Commun*. 2016;7:749–768;
(f) Dansena H, Hj D, Chandrakar K. *J Asian Pharm Clin Res*. 2015;8:171–177.
2. (a) For recent examples see: Cui J, Jin J, Chaudhary AS, et al. *ChemMedChem*. 2016;11:43–56;
(b) Hammer SG, Gobleder S, Naporra F, et al. *Bioorg Med Chem Lett*. 2016;26:292–300;
(c) Loksha YM, Pedersen E, La Colla P, Loddo R. *Org Biomol Chem*. 2016;14:940–946;
(d) Bold G, Schnell C, Furet P, et al. *J Med Chem*. 2016;59:132–146.
3. (a) Brown DJ. In: Taylor EC, Weissberger A, editors. *The Chemistry of Heterocyclic Compounds: The Pyrimidines*, Vol. 52. New York: John Wiley & Sons, Inc.; 1994:329–437;
(b) . for recent examples seeNeumann CN, Hooker JM, Ritter T. *Nature*. 2016;534:369–373;
(c) Maiden TMM, Swanson S, Procopiou PA, Harrity JPA. *Chem A Eur J*. 2015;21:14342–14346;
(d) Chaube UJ, Vyas VK, Bhatt HG. *RSC Adv*. 2016;6:10285–10297;
(e) Fan J, Dai Y, Shao J, et al. *Bioorg Med Chem Lett*. 2016;26:2594–2599;
(f) Okuda K, Zhang Y-X, Hirota T, Sasaki K. *J Heterocycl Chem*. 2015;52:888–895.
4. (a) Sedenkova KN, Averina EB, Grishin YK, et al. *J Org Chem*. 2012;77:9893–9899;
(b) Sedenkova KN, Averina EB, Grishin YK, Kuznetsova TS, Zefirov NS. *Tetrahedron Lett*. 2014;55:483–485;
(c) Sedenkova KN, Averina EB, Grishin YK, et al. *Tetrahedron Lett*. 2015;56:4927–4930;
(d) Sedenkova KN, Dueva EV, Averina EB, et al. *Org Biomol Chem*. 2015;13:3406–3415.
5. (a) Lin ST, Lin LH, Yao YF. *Tetrahedron Lett*. 1992;21:3155–3156;
(b) Lin ST, Kuo SH, Yang FM. *J Org Chem*. 1997;62:5229–5231;
(c) Bondarenko OB, Gavrilova AYu, Murodov DS, Zefirov NS, Zyk NV. *Russ J Org Chem*. 2013;49:186–194 (Zh. Org. Khim. 2013, 49, 198–206).
6. *General procedure for the preparation of tetrahydroquinazoline N-oxides* ***3a–g***. To a mixture of fuming HNO_3 (0.08 mL, 2 mmol) and HSO_3CF_3 (0.18 mL, 2.0 mmol) a solution of dichlorocyclopropane **1** (165 mg, 1.0 mmol) in the corresponding nitrile (1 mL) was added at 10 °C. The reaction mixture was stirred for 7 d at r.t. After treatment with an equal amount of saturated aqueous NaHCO3, the organic phase was separated and the water phase extracted with DCM (3 × 5 mL). The combined organic layers were washed with saturated aqueous NaHCO3 (5 × 5 mL) and dried over $MgSO_4$. The solvent was evaporated in vacuo to give the corresponding *N*-oxide. The product was

isolated via preparative column chromatography on alumina (petroleum ether-CH_2Cl_2).

7. *Chloro-2-methyl-5,6,7,8-tetrahydroquinazoline 1-oxide (**3a**).* Yield 79 mg (40%); yellowish oil; R_f 0.1 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.75–1.94 (m, 4H, 2 CH_2), 2.68 (s, 3H, CH_3), 2.71 (br t, 2H, $^3J_{HH}$ 6.3, CH_2), 2.90 (br t, 2H, $^3J_{HH}$ 6.3, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.6 (CH_3), 20.7 (CH_2), 20.9 (CH_2), 25.2 (CH_2), 25.7 (CH_2), 128.2 (C4a), 144.2 (CCl), 156.4 (C2), 157.2 (C8a). HRMS (ESI$^+$, 70 eV, *m*/*z*): calcd. for $C_9H_{11}ClN_2O$ [M+H]: 199.0633, found: 199.0635.
8. The process of nitro group reduction due to formation of the chlorine cation is responsible for the further transformation of intermediate **A** into the heterocycles **2** or **3**.
9. (a) Becke AD. *J Chem Phys*. 1993;98:5648–5652;
   (b) Lee C, Yang W, Parr RG. *Phys Rev B*. 1988;37:785–789.
10. (a) McLean AD, Chandler GS. *J Chem Phys*. 1980;72:5639–5648;
    (b) Raghavachari K, Binkley JS, Seeger R, Pople JA. *J Chem Phys*. 1980;72:650–654;
    (c) Clark T, Chandrasekhar J, Spitznagel GW, Schleyer PVR. *J Comp Chem*. 1983;4:294–301;
    (d) Frisch MJ, Pople JA, Binkley JS. *J Chem Phys*. 1984;80:3265–3269.
11. Frisch MJ, Trucks GW, Schlegel HB, et al. *Gaussian 09 (Revision E.01)*. Wallingford, CT: Gaussian Inc.; 2016.
12. (a) Fukui K. *Acc Chem Res*. 1981;14:363–368;
    (b) Hratchian HP, Schlegel HB. In: Dykstra CE, Frenking G, Kim KS, Scuseria G, eds. *Theory and Applications of Computational Chemistry: The First 40 Years*. Amsterdam: Elsevier; 2005:195–249.
13. (a) Bodrikov IV, Michurin AN, Vasyanina GI, Bochkareva NN, Krasnoj VL. *J Org Chem USSR (Engl Trans)*. 1980;16:2123–2133 (Zh. Org. Khim. 1980, 16, 2492–2503);
    (b) Habibi Z, Salehi P, Ali Zolfigol M, Yousefi M. *Synlett*. 2007;812–814.
14. CCDC-1483275 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
15. The analogous 4-fluoropyrimidine substituted N-oxide was not obtained, since 6-bromo-6-fluorobicyclo[3.1.0]hexane rapidly decomposed under the reaction conditions and could not be involved in the heterocyclization.