A Journal of the Gesellschaft Deutscher Chemiker
Angewandte Chemie
International Edition
www.angewandte.org

Accepted Article

Title: Design of Trifluoroalkenyliodonium salts for Hypervalency Aided Alkenylation-Cyclization Strategy: Metal-free Construction of Aziridine Ring

Authors: Zoltán Novák, Ádám Mészáros, Anna Székely, and András Stirling

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201802347
Angew. Chem. 10.1002/ange.201802347

Link to VoR: http://dx.doi.org/10.1002/anie.201802347
http://dx.doi.org/10.1002/ange.201802347

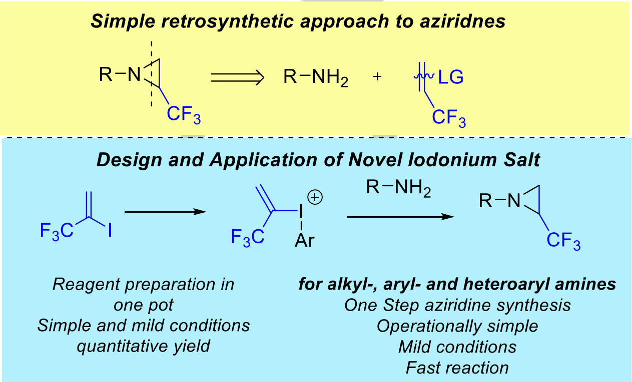
WILEY-VCH

Angewandte Chemie International Edition 10.1002/anie.201802347

Design of Trifluoroalkenyliodonium salts for Hypervalency Aided Alkenylation-Cyclization Strategy: Metal-free Construction of Aziridine Ring

Ádám Mészáros,[a] Anna Székely,[a,b] András Stirling,[c*] Zoltán Novák[a*]

Abstract: Synthesis of fluorinated compounds and their use as pharmaceutical ingredients or synthetic building blocks are in the focus of chemical and medicinal research. However, the efficient synthesis of trifluoromethylated nitrogen heterocycles sometimes are challenging. Herein, we disclose a simple aziridination process which relies on the use of amines and novel alkenyl synthon for the access of trifluoromethylated strained heterocycle. With the utilization of a newly designed, bench stable but highly reactive hypervalent alkenyl iodonium species, the three membered heterocyclic ring can be constructed from simple amines without structural limitation with high efficiency under mild conditions in the absence of transition metal catalysts. The special reactivity of the new trifluoropropenyl synthon toward nucleophilic centres could be exploited in more general cyclization and alkenylation reactions in the future.

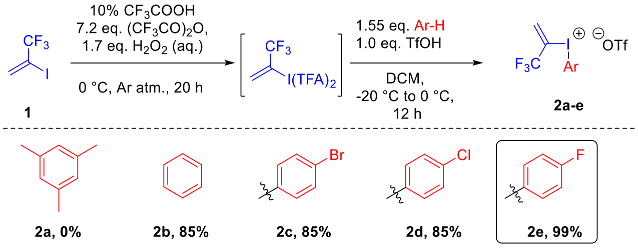


Scheme 1. Trifluoromethylaziridine synthesis from amines and propenyliodonium salts.

Trifluoromethylated organic molecules have accentuated importance in the field of medicinal chemistry due to their beneficial physical, chemical and biological properties such as metabolic stability, lipophilicity and blood-brain barrier penetration.[1] Thus, the introduction of the fluoroalkyl group into different molecular scaffolds is one of the most intensively studied field of organic chemistry.[2] Beside the development of trifluoromethylation processes the construction of small building blocks decorated with fluoroalkyl function is also in the focus of chemical synthesis.[1e, 3] Aziridines belong to these building blocks and a broad range of synthetic approaches are available for the construction[4] and organic transformation[5] of this three membered heterocycle. However, there are some synthetic limitations of the access of 2-trifluoromethylated counterpart.[6] Among many synthetic approaches the highest structural versatility of the synthesized substituted aziridine frame can be achieved with the reaction of amines and C_2-CF_3 synthons [7] to obtain the desired 2-trifluoromethylaziridine building block. Although these synthetic possibilities ensure the best available routes to date, most of them include multistep procedures with transformations, require long reaction times or harsh reaction conditions. More importantly, from mechanistic aspects the major limitation of this ring construction is that only aliphatic amines are applicable for the synthesis.

To circumvent this limitation, we aimed to design novel C2-CF_3 synthon, which is easily and efficiently available from simple raw materials, and reacts straightforwardly with a wide range of amines as the simplest N-R source for the aziridine ring (Scheme 1). We envisioned that the utilization of trifluoropropene skeleton equipped with an aryliodonium[8] leaving group could be the key to open new synthetic possibilities. Our quantum chemical calculations (*vide infra*) regarding the reaction mechanism clearly showed that the utilization of aryliodonium leaving groups could lower the activation energy of the rate determining ring closure step by 10-19 kcal/mol compared to other existing leaving groups such as Cl-, Br-, I-, Ar_2S^+.[9] This rate accelerating ability of the iodonium leaving group could enable the rapid formation of the aziridine ring under mild conditions even in the case of the challenging aromatic amines.

Although the alkenyl iodonium species are known compounds,[10] their synthetic availability is more limited compared to the frequently used diaryliodonium derivatives.[11] As a part of our ongoing research program focusing on the study of fluorinated hypervalent iodonium species,[12] we aimed to design novel trifluoropropenyl iodonium salt as carbon synthon for the construction of the targeted small heterocycle.



Scheme 2. General synthesis for 3,3,3-trifluoromethylpropenyl aryl iodonium salts

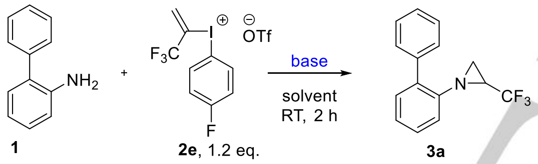
---

[a] Á. Mészáros, Dr. A. Székely, Dr. Z. Novák
ELTE "Lendület" Catalysis and Organic Synthesis Research Group, Institute of Chemistry, Eötvös University, Faculty of Science, Pázmány Péter stny. 1/A, H-1117 Budapest (Hungary)
E-mail: novakz@elte.hu
web: http://zng.elte.hu/
[b] Dr. A. Székely
Current address: Max Planck Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 2, 45470 Mülheim an der Ruhr, Germany
[c] Dr. A. Stirling
Theoretical Chemistry Research Group, Institute of Organic Chemistry, Research Centre for Natural Sciences, Budapest, Magyar tudósok körútja 2., Hungary
Email: stirling.andras@ttk.mta.hu.

10.1002/anie.201802347

Considering the aims of the synthetic studies, the successfully prepared new iodonium salt was reacted with primary amine to explore the chemical behavior of the salt toward nucleophilic species. 2-Aminobiphenyl was chosen as aniline derivative for the optimization studies, which focused on the solvent, base and stoichiometry to reach full conversion at ambient temperature (Table 1.). We were pleased to observe the formation of the three membered heterocycle as the only product in the reaction of the aromatic amine and the alkenyliodonium salt. We found that dichloromethane and diethyl ether were superior as solvent and the appropriate aziridine (**3a**) was isolated in 82% after the reaction reached complete conversion in the presence of Na_2CO_3 base 25°C after 2 hours (entries 1-2). We found that the reaction could also be carried out in acetonitrile, THF and ethyl acetate as well using similar reaction conditions, however, with lower isolated yields (57%, 59%, and 74% respectively, entries 3-5) of the product. The study of the base effect revealed the importance of this additive on the reaction (in the absence of base only 42% yield was reached, entry 6). Amongst the tested bases (NaOH, Na_2CO_3, K_2CO_3, K_3PO_4, triethylamine, pyridine – entries 7-11) sodium carbonate proved to be the optimal choice for the neutralization of the forming trifluoromethanesulfonic acid byproduct, considering the efficiency of the reaction, economy, handling and environmental issues.

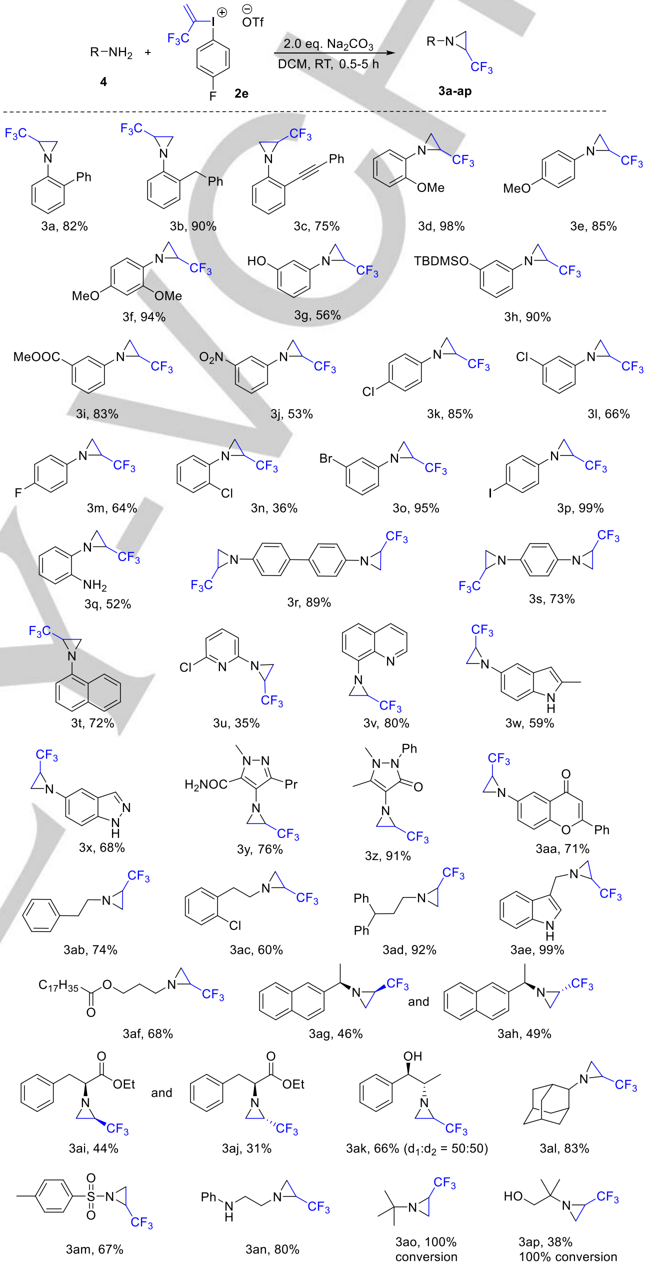
Table 1. Optimization studies.[a]



Entry	Reagent	Base	Solvent	Yield %[b]
1	**2e**	**Na_2CO_3**	**CH_2Cl_2**	**82%**
2	**2e**	**Na_2CO_3**	**Et_2O**	**82%**
3	**2e**	Na_2CO_3	MeCN	74%
4	**2e**	Na_2CO_3	THF	57%
5	**2e**	Na_2CO_3	EtOAc	59%
6	**2e**	-	CH_2Cl_2	42%
7	**2e**	NaOH	CH_2Cl_2	71%
8	**2e**	K_2CO_3	CH_2Cl_2	80%
9	**2e**	K_3PO_4	CH_2Cl_2	60%
10	**2e**	Triethylamine	CH_2Cl_2	0%[c]
11	**2e**	Pyridine	CH_2Cl_2	32%[c]
12	**2b**	**Na_2CO_3**	**CH_2Cl_2**	80%
13	**2c**	**Na_2CO_3**	**CH_2Cl_2**	75%
14	**2d**	**Na_2CO_3**	**CH_2Cl_2**	79%

[a] Reaction conditions: biphenylamine (0.2 mmol, 1 equiv), **2e** (1.2 equiv), base (2.0 equiv), solvent (2.0 mL, c=0.1 mmol/mL), 25 °C, 2 hours [b] isolated yield [c] conversion determined by GC.

The optimized reaction conditions were used for the exploration of the scope and limitation of the methodology. Beyond 2-aminobiphenyl, further substituted aromatic amines with various electronic and steric properties were reacted with the iodonium salt in DCM at 25 °C to prepare *N*-arylated 2-trifluoromethylaziridines. Benzyl, phenylethynyl and methoxy groups at the *ortho* position were well tolerated and we obtained aziridines **3b-d** in 90%, 75% and 98% yields respectively.



Scheme 3. Synthesis of *N*-trifluoromethylaziridines[a] [a] Reaction conditions: amine (0.2-0.3 mmol, 1 equiv), **2e** (1.2 equiv), Na_2CO_3 (2.0 equiv), DCM or THF (2.0 - 3.0 mL, 0.1 mmol amine/1.0 mL solvent), 25 °C, 0.5-5 hours.

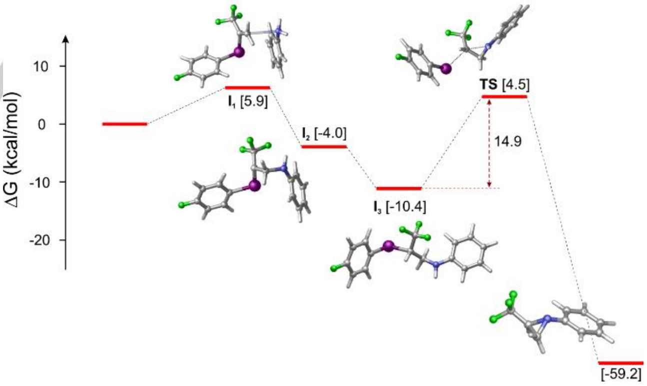
Additionally, the presence of strongly electron donating methoxy groups in other positions on the aryl ring ensured also high yields (**3e-f**, 85% and 94%). However, free hydroxyl group on the aryl ring caused a significant drop of the yield (**3g**, 56%). Installation of simple silyl protecting group onto hydroxyl function solves the difficulties originated supposedly from side reactions or decompositions, and aziridine **3h** was isolated in excellent 90% yield. Electron deficient 3-nitroaniline was also applicable substrate for the transformation but in this case aziridine **3j** was isolated only in 53% yield. However, aniline substrate containing methyl ester function at the *meta* position provided the aziridine **3i** in a good 83% yield.

Next, the representative collection of halogenated aniline derivatives was subjected for the transformation. *Ortho*, *meta* and *para* isomers of fluoro, chloro, bromo and iodo anilines were used for this study and we did not find any lack of the reactivity, and products **3k**-**p** were isolated in good to excellent yields. However, in case of fluorinated and chlorinated products the yield of isolated products was systematically lower than their bromo and iodo analog, due their higher volatility. Bifunctional anilines were selectively mono- or diaziridinated, controlling the selectivity with the stoichiometry of the reactants. First, only one of the amino groups of *ortho* phenylene diamine was converted to aziridine (**3q**, 68%), then in another reaction both amino functions in phenylene diamine were transformed to the three membered heterocycle efficiently (**3r** and **3s**, 89% and 73%). 1-naphthylamine reacted straightforwardly with the iodonium salt and aziridine **3t** was isolated in 72% yield.

To expand further the scope, we used versatile heterocyclic scaffolds for our studies. Amino group attached to pyridine and quinoline ring also enabled the transformation. However, the reaction of 2-aminopyridine derivative provided significantly lower yield compared to the transformation of 8-aminoquinoline (35% **3u** vs. 80% **3v**). NH_2 group of other nitrogen heterocyclic compounds were also smoothly transformed to trifluoromethylaziridine function. The appropriate trifluoromethylaziridyl indazole **3x** was prepared in 59% yield while amino pyrazole and pyrazolone derivatives provided the **3y** and **3z** aziridinyl products in 76% and 91% yield respectively. Amino-chromenone was also successfully subjected to the reaction and the **3aa** aziridine derivative was obtained in 71% yield.

After the reactivity study of aromatic and heteroaromatic amines toward the trifluoroalkenyliodonium salt we utilized several aliphatic amines as substrates under the optimal reaction conditions. Substituted phenethylamines, diphenylpropylamines, tryptamine underwent smooth aziridination and products **3ab-ae** were obtained in 74-99% yield range. The presence of ester function was also tolerated in case of aliphatic amines and aziridine **3af** was isolated in 68% yield. Chiral amines, where the amino group is attached to secondary carbon center such as (*R*)-(+)-1-(2-naphthyl)ethylamine, phenylalanine-ethylester and (1*R*,2*S*)-(−)-norephedrine were also investigated in the study. The aziridine ring formation occurred expectedly on each substrate and the formed diastereomers could be successfully separated in the first two cases and the optically pure products **3ag**, **3ah** (46% and 49%) and **3ai**, **3aj** (44% and 31%) were isolated. However, the norephedrine gave relatively lower yield compared to the others, supposedly due to the presence of unprotected hydroxyl group, and the diastereomer pair **3ak** was obtained as an inseparable mixture of isomers. As miscellaneous products we prepared very bulky *N*-adamantyl-aziridine **3al** in 83% yield, *N*-tosylaziridine as electron deficient heterocycle **3am** in 67% yield. We demonstrated the preferential reactivity of primary alkyl amine function over secondary alkyl-aryl amine site in the transformation of *N*-phenyl-ethylenediamine, and aziridine **3an** was obtained in 80% yield. We also demonstrated that bulky primary amines where the nitrogen attached to tertiary carbon center could also be transformed into the desired heterocycle with the iodonium reagent under mild conditions. However, due to the volatility of the products we determined only the GC conversion of *tert*-$BuNH_2$ (100%), and isolated aziridine **3ap** from the reaction of the appropriate aminoalcohol in 38% yield (100% conversion).

In order to obtain insight into the underlying reaction mechanism, density functional calculations have been performed employing the range-separated hybrid ωB97xd functional including dispersion.[13] The possible mechanistic routes have been analyzed in terms of solvation corrected Gibbs free energy values. Scheme 4 shows the free energy profile of the route leading to the formation of the aziridine ring in a simple model reaction of aniline and **2e**.[14] In agreement with earlier findings we obtained that the resting state is when the iodonium salt is in dissociated form.[12a, c] The reaction is initiated by a weak C-N interaction between the iodonium cation and the amine. This interaction increases the acidity of the N-H bond and a subsequent proton exchange from N to the α-C can considerably stabilize this adduct (intermediate $\mathbf{I_1}$ is deprotonated yielding $\mathbf{I_2}$ which forms intermediate $\mathbf{I_3}$ by protonation).[15] In the suitable conformation a nucleophilic substitution takes place and the new C-N bond closes the aziridine ring. This is the rate determining step with a moderate free energy barrier of 14.9 kcal/mol. Then the reaction becomes strongly exergonic and the final proton transfer from N to the base present (Na_2CO_3) brings the system at -59.2 kcal/mol free energy level. (Note that the protonated product is already significantly stable: -28.1 kcal/mol.)[16]



Scheme 4. Free energy profile (in kcal/mol) for aziridine formation. Energy levels are referenced to isolated aniline and the iodonium salt in dissociated state in DCM. The level of the product state is shifted to fit in. Colour code: grey: C; white: H; blue: N; violet: I; green: F. Further details of the calculations and mechanistic implications can be found in the SI.

In summary, we designed a novel trifluoropropenyl synthon for the simple construction of trifluoromethyl aziridines. The successfully synthesized 3,3,3-trifluoropropen-2-yl aryl iodonium triflate reagent enables rapid formation of the target heterocyclic frame in its reaction with wide range of primary amines under mild reaction conditions. The unique reactivity of the hypervalent iodonium species allows the cyclization not only with aliphatic amines but for aromatic and heteroaromatic amines, which notoriously withstand cyclization in case of traditional leaving groups such as halides or sulfonium salts. This finding was supported by the results of quantum chemical calculations focusing on the reaction mechanism and the comparison of reactivity of trifluoropropenyl substrates equipped with different leaving groups. The enhanced reactivity feature of the novel iodonium reagent significantly expands the scope and synthetic utility of the aziridination reaction and could provide access to various important trifluoromethylated building blocks, and gain application in further trifluoropropenylation reactions with C and heteroatom nucleophiles.

Acknowledgements

This work was supported by National Research, Development and Innovation Office (Grant No. K116034 and K125020) and by the János Bolyai Research Scholarship of the Hungarian Academy of Sciences. The authors thank to Ágnes Gömöry for the HRMS measurements and László Burai and Tamás Gáti for the help in the structure determination.

Keywords: Aziridines • Heterocycles • Iodonium salts • Trifluormethyl group • Cyclization

---

[1] a) N. A. Meanwell, *J. Med. Chem.* **2018**, ASAP, DOI: 10.1021/acs.jmedchem.7b01788; b) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. Del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432-2506; c) K. L. Kirk, *Org. Proc. Res. Dev.* **2008**, *12*, 305-321; d) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317* 1881–1886; e) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37,* 320–330; f) F. Meyer, *Chem. Commun.* **2016**, *52*, 3077-3094.

[2] a) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470-477; b) J.-A. Ma, D. Cahard, *J. Fluorine Chem. 128*, 975–996; c) M. Shimizu, T. Hiyama, *Angew. Chem. Int. Ed.* **2005**, *44*, 214–231; d) T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264; e) O. A. Tomashenko, V. V. Grushin, *Chem. Rev.* **2011**, *111*, 4475–4521; f) S. Barata-Vallejo, A. Postigo, *Coord. Chem. Rev.* **2013**, *257*, 3051–3069; g) E. Merino, C. Nevado, *Chem. Soc. Rev.* **2014**, *43*, 6598-6608; h) X. Liu, C. Xu, M. Wang, Q. Liu, *Chem. Rev.* **2015**, *115*, 683–730; i) X. Yang, T. Wu, R. J. Phipps, F. D. Toste, *Chem. Rev.* **2015**, *115*, 826−870; j) C. Alonso, E. M. de Marigorta, G. Rubiales, F. Palacios, *Chem. Rev.* **2015**, *115*, 1847−1935; k) G. K. S. Prakash, P. V. Jog, PP. T. D. Batamack, G. A. Olah, *Science* **2012**, *338*, 1324-1327; l) G. K. S. Prakash, R. Krishnamurthi, G. A. Olah, *J. Am. Chem. Soc.* **1989**¸ *111*, 393-395; m) T. Besset, C. Schneider, D. Cahard, *Angew. Chem. Int. Ed.* **2012**, *51*, 5048-5050; n) Q. Zhao, T. Besset, T. Poisson, J.-P. Bouillon, X. Pannecoucke, *Eur. J. Org. Chem.* **2016**, 76-82; o) T. Besset, T. Poisson, X. Pannecoucke *Chem. Eur. J.* **2014**, *20*, 16830-16845; p) I. Abdiaj, C. Bottecchia, T. Noël *Synthesis* **2017**, *49*, 4978-4985.

[3] a) M. Schlosser, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5432-5446; b) A. A. Gakh, Y. Shermolovich, *Curr. Top. Med. Chem.* **2014**, *14,* 952-965; c) J. Dolfen, S. Kenis, K. Van Hecke, N. De Kimpe, M. D'hooghe, *Chem. Eur. J.* **2014**, *20,* 10650-10653; d) A. V. Shcherbatiuk, O. S. Shyshlyk, D. V. Yarmoliuk, O. V. Shishkin, S. V. Shishkina, V. S. Starova, O. A. Zaporozhets, S. Zozulya, R. Moriev, O. Kravchuk, O. Manoilenko, A. A. Tolmachev, P. K. Mykhailiuk, *Tetrahedron* **2013**, *69*, 3796-3804.

[4] a) J. B. Sweeney, in *Aziridines and Epoxides in Organic Synthesis* (ed. A. K. Yudin) (**2006**); b) G. S. Singh, M. D'hooghe, N. De Kimpe, *Chem. Rev.* **2007**, *107,* 2080-2135; c) Y. Zhu, Q. Wang, R. G. Cornwall, Y. Shi, *Chem. Rev.* **2014**, *114,* 8199-8256; d) L. Degennaro, P. Trinchera, R. Luisi, *Chem. Rev.* **2014**, *114,* 7881-7929; e) D. Tanner, *Angew. Chem. Int. Ed.* **1994**, *33,* 599-619; f) V. K. Aggarwal, E. Alonso, G. Fang, M. Ferrara, G. Hynd, M. Porcelloni, *Angew. Chem. Int. Ed.* **2001**, *40,* 1433-1436; g) H. Gao, Z. Zhou, Z.; D.-H. Kwon, J. J. S. Coombs, N. E. Behnke, D. H. Ess, L. Kurti, *Nat. Chem.* **2017**, *9,* 681-688; h) J. L. Jat, M. P. Paudyal, H. Gao, H.; Q.-L. Xu, M. Yousufuddin, D. Devarajan, D. H. Ess, L. Kurti, J. R. Falck, *Science* **2014**, *343,* 61-65; i) A. McNally, B. Haffemayer, B. S. L. Collins, M. J. Gaunt, *Nature,* **2014**, *510,* 129-133; j) X. Li, S. Yu, F. Wang, B. Wan, *Angew. Chem. Int. Ed.* **2013**, *52,* 2577-2580; k) L.-M. Jin, X. Xu, H. Lu, X. Cui, L. Wojtas, X. P. Zhang, *Angew. Chem. Int. Ed.* **2013**, 5309-5313; l) S. O. Scholz, E. P. Farney, S. Kim, D. M. Bates, T. P. Yoon, *Angew. Chem. Int. Ed.* **2016**, *55,* 2239-2242; m) Z. Ma, Z. Zhou, L. Kürti, *Angew. Chem. Int. Ed.* **2017**, *56,* 9886-9890; n) K. Guthikonda, J. D. du Bois, *J. Am. Chem. Soc.* **2002**, *124,* 13672-13673.

[5] a) B. Wu, J. R. Parquette, T. V. Rajanbabu, *Science* **2009**, *326,* 1662; b) H. Egami, S. Kawamura, A. Miyazaki, M. Sodeoka, *Angew. Chem. Int. Ed.* **2013**, *52,* 7841-7844; c) C. Schneider, *Angew. Chem. Int. Ed.* **2009**, *48,* 2082-2084; d) P. A. Wender, D. Strand, *J. Am. Chem. Soc.* **2009**, *131,* 7528-7529; e) T. A. Moss, D. R. Fenwick, D. J. Dixon, *J. Am. Chem. Soc.* **2008**, *130,* 10076-10077; f) C.-Y. Huang, A. G. Doyle, *J. Am. Chem. Soc.* **2012**, *134,* 9541-9544.

[6] a) F. Wang, N. Zhu, P. Chen, J. Ye, G. Liu, *Angew. Chem. Int. Ed.* **2015**, *54,* 9356-9360; b) Y. Duan, B. Zhou, J. H. Lin, J. Xiao, J. C. *Chem. Commun.* **2015**, *51.* 13127-13130; c) J. Dolfen, N. De Kimpe, M. D'hooghe, *Synlett*, **2016**, *27*, 1486-1510.

[7] a) S. Kenis, M. D'Hooghe, G. Verniest, V. D. Nguyen, T. A. Thi, T. Nguyen, N. De Kimpe, *Org. Biomol. Chem.* **2011**, *9,* 7217-7223; b) M. Moens, N. De Kimpe, M. D'hooghe *J. Org. Chem.* **2014**, *79*, 5558-5568; c) S. Kenis, M, D'Hooghe, G. Verniest, M. Reybroeck, T. A. D. Thi, C. P. The, T. T. Pham, K .W. Törnroos, N. V. Tuyen, N. De Kimpe, *Chem. Eur. J.* **2013**, *19,* 5966-5971; d) T. Cytlak, B. Marciniak, H. Koroniak, *Efficient Preparations of Fluorine Compounds*. Vol. 57 - Synthesis of CF_3-Substituted Aziridine Ring by the Gabriel Reaction. 375-379 (John Wiley & Sons, Inc., **2013**); e) R. Maeda, K. Ooyama, R. Anno, M. Shiosaki, T. Azema, T. Hanamoto, *Org. Lett.* **2010**, *12,* 2548-2550.

[8] a) P. J. Stang, V. V. Zhdankin, R. Tykwinski, N. S. Zefirov, *Tetrahedron Lett.* **1992**, *33*, 1419−1422; b) E. A. Merritt, B. Olofsson, B. *Angew. Chem. Int. Ed.* **2009**, *48*, 9052−9070; c) J. M. Bouma, B. Olofsson, *Chem. Eur. J.* **2012**, *18*, 14242−14245. d) M. Bielawski, B. Olofsson, *Chem. Commun.* **2007**, *25*, 2521−2523; e) M. S. Yusubov, A. V. Maskaev, V. V. Zhdankin, *ARKIVOC* **2011**, 370−409; f) V. V. Zhdankin, Hypervalent Iodine Chemistry: Preparation, Structure, and Synthetic Applications of Polyvalent Iodine Compounds; Wiley: Chichester, U.K., **2013;** g) B. Olofsson, *Topics in Curr. Chem.* **2015**, *373*, 135-166; h) K. Aradi, B. L. Tóth, G. L.; Tolnai, Z. Novák, Z. *Synlett* **2016**, *27*, 1456-1485.

[9] For details see Supporting Information.

[10] a) E. Stridfeldt, A. Seemann, M .J. Bouma, C. Dey, A. Ertan, B. Olofsson, *Chem. Eur. J.* **2016**, *22,* 16066-16070; b) J. Wu, X. Deng, H. Hirao, N. Yoshikai, *J. Am. Chem. Soc.* **2016**, *138,* 9105-9108; c) K. Miyamoto, Y. Yokota, T. Suefuji, K. Yamaguchi, T. Ozawa, M. Ochai, *Chem. Eur. J.* **2014**, *20*, 5447-5453; d) D. Holt, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2015**, *54*, 7857-7861; e) E. Cahard, E. N. Bremeyer, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2013**, *52*, 9284-9288; f) E. Scucas, D. W. C. MacMillan, *J. Am. Chem. Soc.*, **2012**, *134*, 9090–9093; g) J. Sheng, Y. Wang, X. Su, R. He, C. Chen, *Angew. Chem. Int. Ed.,* **2017**, *56*, 4824-4828.

[11] a) M. Bielawski, M. Zhu, B. Olofsson, *Adv. Synth. Catal.* **2007**, *349*, 2610-2618; b) M. Bielawski, D. Aili, B. Olofsson, *J. Org. Chem.* **2008**, *73*, 4602-4607; c) M .Bielawski, J. Malmgren, L. M. Padro, Y. Wikmark, B. Olofsson *ChemistryOpen* **2014**, *3*, 19-22; d) G. Laudadio, H. P. L. Gemoets, V. Hessel, T. Noël *J. Org. Chem.* **2017**, *82*, 11735-11741.

[12] a) G. L. Tolnai, A. Székely, Z. Makó, T. Gáti, J. Daru, T. Bihari, A. Stirling, Z. Novák, *Chem. Commun.* **2015**, *51,* 4488-4491; b) B. L. Tóth, Sz. Kovács, G. Sályi, Z. Novák, *Angew. Chem. Int. Ed.* **2016**, *55,* 1988-1992. c) Sz. Kovács, B. L. Tóth, G. Borsik, T. Bihari, N. V. May, A. Stirling, Z. Novák Z. *Adv. Synth. Catal.* **2017**, *359,* 527-532.

[13] J.-D. Chai, M. Head-Gordon, *PCCP* **2008**, *10*, 6615-6620.

[14] Comparison of energetics of reactions with **2b** and **2e** can be found in the Supporting Information.

[15] For details see Supporting Information. The proton transfer was proved by the aziridination of d7-aniline. 76% Deuterium incorporation was observed in the isolated *N*-phenylaziridine.

[16] Free energy profiles of the formation of thermodynamically more favorable products such as enamines and disubstituted amines were also calculated. Their comparison revealed that the process was kinetically controlled and favored the formation of aziridine ring over the other possible reaction paths. The calculations were supported by the experimental findings. For details see Supporting Information.

Layout 1:

COMMUNICATION

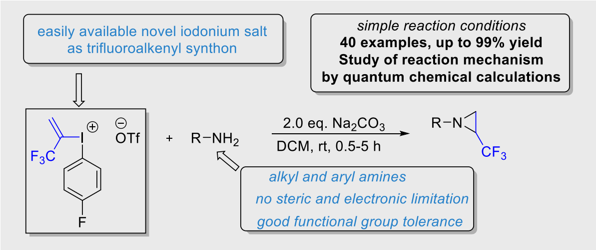
Text for Table of Contents

((Insert TOC Graphic here))

Page No. – Page No.

Layout 2:

COMMUNICATION



Ádám Mészáros, Anna Székely, András Stirling, Zoltán Novák**

Page No. – Page No.

Design of Trifluoroalkenyliodonium salts for Hypervalency Aided Alkenylation-Cyclization Strategy: Metal-free Construction of Aziridine Ring

A bench stable but highly reactive hypervalent trifluoromethylalkenyl iodonium species was designed as novel electrophilic synthon for the functionalization of nucleophilic species such as primary amines. The alkynylation-cyclization strategy enables the efficient transition metal-free construction of aziridine ring under mild conditions in the absence of transition metal catalysts.