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Bastien Michelet, Ugo Castelli, Emeline Appert, Maude Boucher, Kassandra Vitse, et al.. Access to Optically-Pure Benzosultams by Superelectrophilic Activation. *Organic Letters*, 2020, 22 (13), pp.4944-4948. 10.1021/acs.orglett.0c01301 . hal-03016554

HAL Id: hal-03016554

<https://hal.science/hal-03016554>

Submitted on 20 Nov 2020

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Access to Optically-Pure Benzosultams by Superelectrophilic Activation

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Supporting Information Placeholder

ABSTRACT: Through superacid activation, *N*-(arenesulfonyl)-aminoalcohols derived from readily-available ephedrine or amino acids undergo an intramolecular Friedel-Crafts reaction to afford enantiopure benzosultams bearing two adjacent stereocenters in high yields with a fully-controlled diastereoselectivity. Low-temperature NMR spectroscopy demonstrated the crucial role played by the conformationally-restricted chiral dicationic intermediates.

Benzosultams are prominent scaffolds in organic synthesis and have found many applications, especially in medicinal chemistry (**Figure 1**).¹ In light of the growing demand for enantioenriched benzosultam-based therapeutics, versatile methodologies for their synthesis have been developed, including metal-catalyzed asymmetric cyclization, enantioselective addition to *N*-sulfonyl imines, reductive amination or C–H bond amination.² Although demonstrated to be efficient approaches to generate enantioenriched benzosultams exhibiting one stereocenter, expeditious methods to control multiple continuous stereocenters of enantiopure benzosultams are still on demand.³

Figure 1. Selected examples of biologically-active benzosultams.

One of the simplest route to nitrogen-containing heterocycles is probably the intramolecular Friedel-Crafts alkylation of alkenes or alcohols.⁴ We previously demonstrated that under superacid conditions, *N*-allyl-arenesulfonamides cyclize to benzosultams.⁵ This process is promoted by the *in situ* formation of superelectrophilic ammonium-carbenium dications that can react with very poor aromatic nucleophiles such as arenesulfonamides despite the strong deactivating character of the sulfamoyl group (**Figure 2A**).

Figure 2. A. Previous work on superacid-mediated synthesis of racemic benzosultams. **B.** Dihydroisoquinolinone derivative synthesis in concentrated sulfuric acid. **C.** Highly diastereoselective intramolecular Friedel-Crafts alkylation induced by benzylic strain. **D.** Strategy envisioned for the diastereoselective synthesis of optically-pure benzosultams by superelectrophilic activation (this work).

Interestingly, starting from a *N*-aroyl derivative of (–)-ephedrine, Trepanier demonstrated the formation of an enantiopure

dihydroisoquinolinone derivative after reaction in concentrated sulfuric acid (**Figure 2B**).⁶ This reaction suggested the implication of a strong electrophilic benzylic carbocation and motivated this work. By taking advantage of the stability of benzylic carbocations and of benzylic strain, Bach⁷ and others⁸ developed highly diastereoselective inter- and intramolecular reactions that can be considered as guides for further developments (**Figure 2C**). We envisioned that starting from simple *N*-(arenesulfonyl)-ephedrine derivatives **1**, conformationally-restricted dicationic key intermediate **A** could be generated in superacidic conditions. It would react diastereoselectively to furnish enantiopure benzosultams (**Figure 2D**). This strategy would also be amenable to a higher level of complexity starting from amino acids in very few steps, making this method one of the rare examples of enantiopure benzosultams synthesis from the chiral pool.⁹⁻¹²

First, our initial hypothesis was evaluated by testing the reactivity of ephedrine derivative **1a**, bearing a relatively electron-rich tosyl group, to various acidic conditions (**Table 1**).

Table 1. Optimization of the acid-promoted diastereoselective synthesis of benzosultam **2a**.

Entry	Acid	Conditions	[2a] ^a	[2b] ^a
1	HF/SbF ₅ (7/1) ^b	-40 °C, 0.5 h	70%	-
2	TfOH ^b	-40 °C, 0.5 h	70%	-
3	TfOH (2 equiv.)	-40 °C, 16 h	10%	-
4	TfOH (2 equiv.)	20 °C, 0.5 h	- ^c	32% ^d
5	TfOH (2 equiv.)	20 °C, 16 h	-	45% ^d
6	FeCl ₃ (2 equiv.)	-40 °C, 16 h	-	-
7	FeCl ₃ (2 equiv.)	20 °C, 0.5 h	-	48% ^d
8	FeCl ₃ (2 equiv.)	20 °C, 16 h	-	89%
9	FeCl ₃ (1 equiv.)	20 °C, 16 h	-	38%
10	FeCl ₃ (0.1 equiv.)	20 °C, 16 h	-	-
11	AlCl ₃ (2 equiv.)	20 °C, 16 h	-	18%
12	BF ₃ OEt ₂ (2 equiv.)	20 °C, 16 h	-	-
13	CeCl ₃ (2 equiv.)	20 °C, 16 h	-	-
14	Ce(OTf) ₃ (2 equiv.)	20 °C, 16 h	-	-
15	Bi(OTf) ₃ (2 equiv.)	20 °C, 16 h	-	-
16	Sc(OTf) ₃ (2 equiv.)	20 °C, 16 h	-	-
17	H ₂ SO ₄ (95%) ^b	10 °C, 16 h	14%	14%
18	CF ₃ CO ₂ H ^b	-14 °C, 16 h	-	-

^a Yield of isolated product unless stated otherwise. ^b Used as solvent.

^c Traces. ^d Determined by ¹H-NMR analysis using *p*-anisaldehyde as internal standard.

Using neat HF/SbF₅ superacid,⁵ we could obtain the desired cyclized product **2a** after only 30 min at -40 °C in a good 70% yield with a fully-controlled diastereoselectivity (**Table 1**, entry 1). Delightfully, switching HF/SbF₅ to the safer trifluoromethanesulfonic acid allowed to afford **2a** in similar yield and again, as a single diastereomer (**Table 1**, entry 2). However, any attempts of using lower amounts of trifluoromethanesulfonic acid in CH₂Cl₂ led to poor yields or formation of the regioisomer **2b** when the reaction was carried out at higher temperature (**Table 1**, entries 3-5). Such isomerization is a well-known drawback of Friedel-Crafts alkylations and can be explained by intramolecular rearrangement within the arenium ion generated by subsequent protonation of the kinetic product **2a** to the most

stable product **2b**.¹³ Nevertheless, the formation of byproduct **2b** can be prevented by keeping the reaction mixture at -40 °C allowing the isolation of **2a** as a single regio- and stereoisomer.¹⁴ We next evaluated the reactivity of **1a** with excess of Lewis acids. FeCl₃ was found inactive at -40 °C and carrying out the transformation at higher temperature afforded again the undesired regioisomer **2b** (**Table 1**, entries 6-10). The use of other Lewis acids from the main group, transition metal or lanthanide series led to poor yields or no conversion at all (**Table 1**, entries 11-16). Decreasing the protonating ability of the system by running the reaction in sulfuric acid or trifluoroacetic acid was shown to be detrimental to the reaction, a result which supports our initial hypothesis and the necessity to use super-electrophilic activation to perform this transformation (**Table 1**, entries 17-18). In order to avoid the formation of any regioisomeric byproducts and for better reproducibility, we selected the use of neat trifluoromethanesulfonic acid at -40 °C as the optimal conditions (**Table 1**, entry 2).

Figure 3. Reaction scope for the synthesis of enantiopure benzosultams derived from ephedrines. ^a A 63% yield was obtained on 1 g scale (see SI for full details). ^b Major regioisomer depicted with solid bonds; minor regioisomer depicted with dashed bonds. ^c Ellipsoids are drawn at 50% probability level and hydrogen atoms are represented as fixed-size spheres of radius 0.30 Å.

The scope and functional group tolerance of this diastereoselective intramolecular Friedel-Crafts cyclization was next evaluated (**Figure 3**). Ephedrine derivatives **1a-e**, exhibiting alkyl electron-donating groups on the aromatic ring, were smoothly converted to the corresponding enantiopure benzosultams in good to excellent yields. The presence of electron-donating group on the arenesulfonamide is not essential for the cyclization, as shown by the clean conversion of substrate **1f** to its cyclic analogue **2f**. Naphthalene and indane derivatives **2g** and **2h** were also generated in very good yields by exploiting this reaction. The reaction proceeded equally well with electron-rich methoxy-substituted arenesulfonamides affording compounds **2i** and **2j** in excellent yields. Noteworthy, the two regioisomers **2j_p** and **2j_o** could be isolated separately after flash column chromatography. While products **2k-m** were generated in generally lower yields, their formation – which must involve the nucleophilic addition of the halogenated deactivated aromatic rings – further reinforces the hypothesis of the transient formation of a highly reactive cationic intermediate. However, strongly-deactivating substituents such as CF₃, C(O)Me or NO₂ completely inhibited the cyclization (**Figure 3**, bottom). Heteroarene could also be used as nucleophile as exemplified by the preparation of benzosultam **2n**, an analogue of the antiglaucoma agent brinzolamide. Norephedrine derivative **1o**, bearing no methyl group on the nitrogen atom, reacted in the optimized conditions to afford benzosultams **2o**, albeit in moderate yield, opening new synthetic perspectives through further N-functionalizations. The structure and stereochemistry of these chiral compounds were confirmed by X-ray analysis of the collected crystals of **2a** generated after reaction of substrate **1a**.¹⁵ To highlight the versatility of the method and verify the enantiopurity of every products, the reaction was carried out with each enantiomer of starting material. With success, the corresponding cyclic products were generated in enantiopure form in similar yields.

One step further in complexity, substrates bearing more hindered alkyl substituents at the stereogenic center as well as substituents on the phenyl ring were selected (substrates **1p-s**, **Figure 4**). Using the corresponding aminoacids as chiral platform, successive tosylation / reductive amination / reduction / aryl Grignard addition led to the clean formation of enantiomers **1p-r**. A slightly modified procedure from proline derivatives led to the formation of product **1s**. The Grignard addition was fairly diastereoselective (dr from 4.7:1 to > 20:1) and the major *syn* diastereomers **1p-s** could be isolated cleanly by flash chromatography on silica gel.¹⁶

Figure 4. Synthesis of benzosultam precursors **1p-s** from amino acids.

The superacid-promoted cyclization applied to **1p** and **1q** gratifyingly demonstrated the compatibility of the method with halogenated ephedrine derivatives (**Figure 5**). However, substrates exhibiting vinyl or electronically-enriched *p*-methoxyphenyl substituents led only to complex mixture of compounds. In the latter case, the enhanced stability of the postulated benzylic cation seems detrimental to the process, leading to the formation of degradation byproducts upon hydrolysis. Performing this reaction with FeCl₃ (conditions from **Table 1**, entry 8) afforded only *N*-(methyl)tosylamine in 97% yield which confirms the lower reactivity of the cationic intermediate towards Friedel-Crafts alkylation. As illustrated by the transformation of **1r** and **1s**, respectively synthesized from leucine and proline, the diastereoselectivity of the reaction is maintained with bulkier α -substituted amines. Furthermore, the formation of enantiomers **2s** proves the efficiency of this strategy to generate enantiopure conformationally-rigid sultams of interest.¹⁷

Figure 5. Reaction scope for the synthesis of enantiopure benzosultams derived from amino acids.

From a mechanistic point of view, this reaction most-likely proceed through the formation of a benzylic carbocation.^{7d} The stereochemical information borne by the hydroxy-substituted benzylic carbon should therefore play only a minor role in the outcome of the transformation. When the tosyl-pseudoephedrine **1a'** (diastereomer of **1a**) was reacted in the optimized conditions, benzosultam **2a** was isolated in a similar yield (83% vs. 70-77%) as starting from **1a**, thus confirming our hypothesis (**Figure 6A**). Then, we explore the hypothetical formation of any dicationic intermediate in superacid solutions. To this end, preventing the substrate from any cyclization by substituting the arenesulfonyl moiety with a trifluoromethyl group, we initiated our investigation by exploring the behavior of *N*-(arenesulfonyl)ephedrine **1t** in TfOH by low-temperature *in situ* NMR analysis. Unfortunately, in TfOH, no clean ¹H or ¹³C NMR spectra could be collected from this experiment. Considering that the lifetime of the generated cations in these conditions disallow any observation at the NMR time scale, the same experiment was conducted in weaker nucleophilic conditions¹⁸ by submitting the same substrate to HF/SbF₅ superacid solution. In these conditions, ¹H, ¹³C and HSQC NMR analysis of the crude reaction mixture provided strong evidences for the formation of the key dicationic species **A_t** (**Figure 6B**).¹⁹ ¹H NMR spectrum displays a doublet (*J* = 9.7 Hz) at 8.10 ppm characteristic of a carbocationic benzylic C–H bond^{7d} as well as a broad signal at 6.37 ppm attributed to the protonation of the sulfonamide moiety.²⁰ The signal of the *N*-methyl substituent is now a doublet (*J*

= 4.6 Hz) slightly shielded to 1.79 ppm (compared to a singlet at 2.79 ppm for **1t** in CDCl₃). This species is also characterized by a benzylic carbenium ion at 198.4 ppm in the ¹³C NMR spectrum.^{7d, 8d} Interestingly, both ¹H and ¹³C NMR spectra show non-equivalent signals for the phenyl substituent indicating a restriction of rotation around the phenyl–carbocation bond.^{7b} Luckily, the ¹H NMR spectrum was sufficiently well-resolved to allow a NOESY experiment which showed a correlation between the benzylic proton and an aromatic ortho proton as well as a correlation between the proton at the stereogenic center and another aromatic ortho proton. Altogether, these NMR observations supported our initial hypothesis on the generation of conformationally-restricted superelectrophiles in superacid. The carbon atom in para position displays a strong downfield shift to 168.1 ppm (compared to 128.1 ppm for **1t** in CDCl₃) indicating a strong delocalization of the positive charge to this carbon atom. This observation might be explained by the propensity of the aryl group to tackle the destabilization of the benzylic carbocation induced by the proximity of the second cationic charge located on the nitrogen atom.^{8d} Collectively, these data suggest that a right balance between conformational stabilization and sufficient electrophilic character must exist to favor the intramolecular diastereoselective nucleophilic substitution.

Figure 6. A. Synthesis of benzosultam **2a** from tosyl-pseudoephedrine **1a'**. B. Low-temperature ¹H NMR (top) and ¹³C NMR (bottom) analysis of ephedrine derivative **1t** in HF/SbF₅ (1/1) at -40 °C. Acetone-*d*₆ is used as external standard.

To conclude, taking advantage of the chiral pool, a series of optically-active *N*-(arenesulfonyl)-aminoalcohols were efficiently converted to enantiopure benzosultams exhibiting a wide array of functions and substitution patterns. Demonstrated by low-temperature NMR spectroscopy, this process exploits the super-electrophilic character and the privileged conformation of chiral benzylic dications in superacidic solution.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

General experimental procedures, reaction setup, characterization data, low-temperature NMR spectra and spectra for all key compounds (PDF).

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

ACKNOWLEDGMENT

We great fully acknowledge the French Ministry of research and education for PhD grant (for U.C.). We also acknowledge the University of Poitiers, the Centre National de la Recherche Scientifique, the European Union (ERDF), the Région Nouvelle-Aquitaine and the French Fluorine Network.

REFERENCES

- (1) For recent selected examples, see: (a) Tang, J.; Chen, H.; He, Y.; Sheng, W.; Bai, Q.; Wang, H. *Nat. Commun.* **2018**, 9, 3383. (b) Aldrich, L. N.; Kuo, S.-Y.; Castoreno, A. B.; Goel, G.; Kumballa, P.; Rees, M. G.; Seashore-Ludlow, B. A.; Cheah, J. H.; Latorre, I. J.; Schreiber, S. L.; Shamji, A. F.; Xavier, R. J. *J. Am. Chem. Soc.* **2015**, 137, 5563. (c) Shan, W.; Balog, A.; Nation, A.; Zhu, X.; Chen, J.; Cvijic, M. E.; Geng, J.; Rizzo, C. A.; Spiers Jr., T.; Attar, R. M.; Obermeier, M.; Traeger, S.; Dai, J.; Zhang, Y.; Galella, M.; Trainor, G.; Vite, G. D.; Gavai, A. V. *Bioorg. Med. Chem. Lett.* **2016**, 26, 5707. (d) Desbordes, P.; Dubost, C.; Dufour, J.; Gourgues, M.; Holstein, P.; Lempeur, V.; Mieg, F.; Rinolfi, P.; Rodeschini, V.; Toquin, V.; Villalba, F.; Wachendorff-Neumann, U.; WO2018007323, **2018**. (e) Liu, F.; Martin-Mingot, A.; Lecornué, F.; Jouanetaud, M.-P.; Maresca, A.; Thibaudau, S.; Supuran, C. T. *J. Enz. Inhib. Med. Chem.* **2012**, 27, 886.
- (2) For recent reviews, see: (a) Majumdar, K. C.; Mondal, S. *Chem. Rev.* **2011**, 111, 7749. (b) Debnath, S.; Mondal, S. *Eur. J. Org. Chem.* **2018**, 8, 933. For recent selected examples, see: (c) Song, B.; Yu, C.-B.; Ji, Y.; Chen, M.-W.; Zhou, Y.-G. *Chem. Commun.* **2017**, 53, 1704. (d) Sun, Y.-T.; Zhu, D.-X.; Rao, X.; Xu, M.-H.; *Org. Chem. Front.* **2020**, 7, 340. (e) Hu, Y.; Lang, K.; Li, C.; Gill, J. B.; Kim, I.; Lu, H.; Fields, K. B.;

- Marshall, M.; Cheng, Q.; Cui, X.; Wojtas, L.; Zhang, X. P. *J. Am. Chem. Soc.* **2019**, *141*, 18160.
- (3) For the recently reported rare examples, see: (a) Hou, L.; Kang, T.; Yang, L.; Cao, W.; Feng, X. *Org. Lett.* **2020**, *22*, 1390. (b) Pan, J.; Wu, J.-H.; Zhang, H.; Ren, X.; Tan, J.-P.; Zhu, L.; Zhang, H.-S.; Jiang, C.; Wang, T. *Angew. Chem. Int. Ed.* **2019**, *58*, 7425. (c) Chen, Y.-H.; Lv, X.-J.; You, Z.-H.; Liu, Y.-K. *Org. Lett.* **2019**, *21*, 5556. (d) Song, B.; Chen, M.-W.; Zhou, Y.-G. *Org. Chem. Front.* **2018**, *5*, 1113. (e) Jeran, M.; Cotman, A. E.; Stephan, M.; Mohar, B. *Org. Lett.* **2017**, *19*, 2042.
- (4) (a) Rueping, M.; Nachtsheim, B. J. *Belstein J. Org. Chem.* **2010**, *6*, 6. (b) Heravi, M. M.; Zadsirian, V.; Saedi, P.; Momeni, T. *RSC Adv.* **2018**, *8*, 40061. (c) Naredla, R. R.; Klumpp, D. *Chem. Rev.* **2013**, *113*, 6905.
- (5) Liu, F.; Martin-Mingot, A.; Jouannetaud M.-P.; Zunino, F.; Thibaudeau, S. *Org. Lett.* **2010**, *12*, 868.
- (6) Trepanier, D. L.; Sunder, S. *J. Med. Chem.* **1973**, *16*, 342.
- (7) (a) Mühlthau, F.; Schuster, O.; Bach, T. *J. Am. Chem. Soc.* **2005**, *127*, 9348. (b) Mühlthau, F.; Stadler, D.; Goepfert, A.; Olah, G. A.; Prakash, G. K. S.; Bach, T. *J. Am. Chem. Soc.* **2006**, *128*, 9668. (c) Stadler, D.; Bach, T. *Chem. Asian J.* **2008**, *3*, 272. (d) Stadler, D.; Goepfert, A.; Rasul, G.; Olah, G. A.; Prakash, G. K. S.; Bach, T. *J. Org. Chem.* **2009**, *74*, 312. (e) Rubenbauer, P.; Bach, T. *Chem. Commun.* **2009**, 2130. (f) Stadler, D.; Mühlthau, F.; Rubenbauer, P.; Herdtweck, E.; Bach, T. *Synlett* **2006**, *16*, 2573.
- (8) (a) Chung, J. Y. L.; Mancheno, D.; Dormer, P. G.; Variankaval, N.; Ball, R. G.; Tsou, N. N. *Org. Lett.* **2008**, *10*, 3037. (b) Chung, J. Y. L.; Steinhuebel, D.; Krska, S. W.; Hartner, F. W.; Cai, C.; Rosen, J.; Mancheno, D. E.; Pei, T.; DiMichele, L.; Ball, R. G.; Chen, C.; Tan, L.; Alorati, A. D.; Brewer, S. E.; Scott, J. P. *Org. Process Res. Dev.* **2012**, *16*, 1832. (c) Chénard, E.; Hanessian, S. *Org. Lett.* **2014**, *16*, 2668. For an earlier report on Friedel-Crafts reactions of ephedrine derivatives with benzene, see: (d) Klumpp, D. A.; Aguirre, S. L.; Sanchez, G. V.; de Leon, S. J. *Org. Lett.* **2001**, *3*, 2781.
- (9) (a) Rayabarapu, D. K.; Zhou, A.; Jeon, K. O.; Samarakoon, T.; Rolfe, A.; Siddiqui, H.; Hanson, P. R. *Tetrahedron* **2009**, *65*, 3180. (b) Ullah, F.; Samarakoon, T.; Rolfe, A.; Kurtz, R. D.; Hanson, P. R.; Organ, M. G. *Chem. Eur. J.* **2010**, *16*, 10959. (c) Rolfe, A.; Samarakoon, T. B.; Hanson, P. R. *Org. Lett.* **2010**, *12*, 1216. (d) Loh, J. K.; Asad, N.; Samarakoon, T. B.; Hanson, P. R. *J. Org. Chem.* **2015**, *80*, 9926. (e) Faisal, S.; Maity, P. K.; Zang, Q.; Samarakoon, T. B.; Sourk, R. L.; Hanson, P. R. *ACS Comb. Sci.* **2016**, *18*, 387.
- (10) (a) Chen, W.; Li, Z.; Oua, L.; Giulianotti, M. A.; Houghten, R. A.; Yu, Y. *Tetrahedron Lett.* **2011**, *52*, 1456. (b) Dadiboyena, S.; Nefzi, A. *Tetrahedron Lett.* **2012**, *53*, 6897. (c) Foschi, F.; Tagliabue, A.; Mihali, V.; Pilati, T.; Pecnikaj, I.; Pensio, M. *Org. Lett.* **2013**, *15*, 3686.
- (11) Ishida, N.; Shimamoto, Y.; Yano, T.; Murakami, M. *J. Am. Chem. Soc.* **2013**, *135*, 19103.
- (12) Laha, J. K.; Jethava, K. P.; Dayal, N. *J. Org. Chem.* **2014**, *79*, 8010.
- (13) Olah, G. A.; Farooq, O.; Farnia, S. M. F.; Olah, J. A. *J. Am. Chem. Soc.* **1988**, *110*, 2560.
- (14) Partial isomerization was observed with TfOH or FeCl₃ even at -20 °C; data not shown.
- (15) CCDC 1994486 (**2a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
- (16) See SI for more information.
- (17) Blahun, O. P.; Rozhenko, A. B.; Rusanov, E.; Zherish, S.; Tolmachev, A. A.; Volochnyuk, D. M.; Grygorenko, O. O. *J. Org. Chem.* **2020**, doi: 10.1021/acs.joc.9b03394.
- (18) Krossing, I.; Raabe, I. *Angew. Chem. Int. Ed.* **2004**, *43*, 2066.
- (19) See SI for full NMR spectra.
- (20) Birchall, T.; Gillespie, R. J. *Can. J. Chem.* **1963**, *41*, 2642.