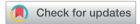
# **RSC Advances**



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# Transformation of 5-acylated N-fluoroalkyl-1,2,3-triazoles to trifluoromethylated ring-fused isoquinolines, 1,3-oxazines, and 1,3-oxazin-6-ones via ketenimines†

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A one-pot multistep methodology leading to trifluoromethylated cyclopenta[c]isoquinolines, indeno[1,2-c] isoquinolines, 6,6-difluoro-1,3-oxazines, or 1,3-oxazin-6-ones, based on the reaction of 5-acylated *N*-pentafluoroethyl-substituted 1,2,3-triazoles is presented. A thermal ring opening of the starting triazoles, followed by a 1,2-acyl shift formed reactive ketenimines which cyclized after a rearrangement in a substrate-specific manner to provide new trifluoromethylated heterocyclic products.

## Introduction

Isoquinolines with fused 5-membered rings, 6H-1,3-oxazines, or oxazin-6-ones constitute important classes of biologically active compounds known as anti-tubercular, anti-inflammatory, sedative agents, or enzyme inhibitors (Fig. 1).1-5 Despite the few known synthetic strategies to indeno[1,2-c]isoquinolines<sup>1,6-8</sup> or cyclopenta[c]isoquinolines,9 the preparation of 2trifluoromethyl-5-membered ring-fused isoquinolines was described for only one specific example.10 Similarly, nonfluorinated fully substituted 6H-1,3-oxazin-6-ones can be synthesized from β-lactams, isoxazolones, isoxazolones, propenones<sup>15</sup> or ynamides.<sup>16</sup> However, 2-trifluoromethylsubstituted 1,3-oxazin-6-ones or 1,3-oxazines remain unexplored (Fig. 1). Since trifluoromethylated heteroaromatics of novel structures are highly valued chemicals, which find use in medicinal chemistry117-20 and agrochemistry21-23 research programmes, we set out to investigate the synthetic approaches towards the proposed novel trifluoromethylated heteroarenes shown in Fig. 1.

We recently reported a denitrogenation strategy for multisubstituted *N*-fluoroalkylated 1,2,3-triazoles<sup>24-31</sup> with Brønsted or Lewis acids proceeding *via* vinyl cation intermediates and leading to various *N*-alkenyl compounds.<sup>10,24,30-32</sup> We also showed that *N*-fluoroalkyl 1,2,3-triazoles in microwave reaction Herein, we propose a new synthetic methodology to prepare trifluoromethylated 5-membered ring fused isoquinolines, 6,6-difluoro-1,3-oxazines or 1,3-oxazin-6-ones from 5-acyl-*N*-pentafluoroethyl-1,2,3-triazoles involving ketenimine intermediates (Scheme 1).

### Results and discussion

Denitrogenation of *N*-fluoroalkylated 1,2,3-triazoles to ketenimines by microwave heating<sup>33</sup> was extended to 5-acylated

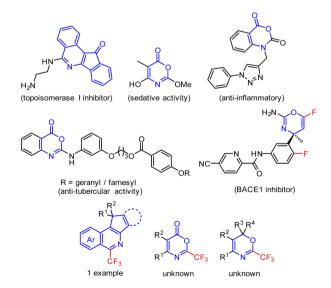


Fig. 1 Selected examples of bioactive 5-membered ring fused isoquinolines or 1,3-oxazine and 1,3-oxazin-6-ones and compounds of interest – their trifluoromethylated derivatives.

conditions undergo a rearrangement to form ketenimines,<sup>33</sup> which can further cyclize to isoquinolines (Scheme 1).<sup>34</sup>

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**Scheme 1** Microwave-assisted transformation of *N*-penta-fluoroethyl-1,2,3-triazoles to trifluoromethylated isoquinolines *via* ketenimines (previous work) or to (fused)isoquinolines, 1,3-oxazines, or 1,3-oxazin-6-ones (this work).

triazoles.<sup>24</sup> Thus, microwave heating of 5-methacryloyl-substituted triazole **1a** resulted in the formation of a mixture of ring-fused 1-trifluoromethylisoquinolines **2a** and **3a**, presumably *via* ketenimine **A**, imidoyl fluoride **B** and isoquinoline C intermediates (Table 1, entry 1). The addition of fluoride salts can enhance the 1,3-fluorine shift of **A** to **B**, therefore an optimization study was conducted to improve the selectivity of the reaction. Copper(II) fluoride was identified as the most effective fluoride additive (entry 8). A combination of potassium fluoride and sodium hydroxide was used to obtain dehydrofluorinated 1-trifluoromethyl-isoquinoline **3a** (entry 9).

A small library of 4-aryl-5-methacryloyl triazoles, obtained from the intercepted click reaction of aromatic copper(1) acetylides, azidopentafluoroethane and methacrylic chloride in the presence of DIPEA (see ESI† for details), was subjected to

the reaction providing ring-fused isoquinolines 2 in moderate to good yields (Scheme 2). The structure of derivative 2c was confirmed by crystallography. Substrate with electronacceptor group (nitro) on the aryl ring did not form the product (2e). Additionally, two examples of dehydrofluorinated isoquinolines 3 were prepared albeit in moderate to low yields.

When electron-rich 5-(3,5-dimethoxybenzoyl)-substituted 1,2,3-triazoles were used, ring-fused 1-trifluoromethylisoquinolines 4 bearing various substituents on the isoquinoline ring formed in good yields (Scheme 2).

All other investigated 5-acylated 1,2,3-triazoles except 5-(3,5-dimethoxybenzoyl)strongly electron-rich methacryloyl-substituted ones afforded different products under the thermal denitrogenation conditions. Thus, 5-(4methoxyphenyl)-substituted triazole underwent a unique transformation presumably via ketenimine D, followed by 1,3aryl group transfer to ketene E,35 1,5-fluorine shift to intermediate F, and cyclization involving another 1,5-fluorine shift to 6,6-difluoro-2-trifluoromethyl-1,3-oxazine 5a or a product of its hydrolysis 1,3-oxazin-6-one 6a (Table 2). Short reaction time (5 min) and no additive favoured the formation of product 5a, while a longer reaction time (20 min) and the use of CuF2 favoured the product of hydrolysis 6a. Four examples of 1,3-oxazines 5 were prepared in moderate to good yields, including the crystal structure of 5c and nine examples of 1,3-oxazinones 6 were synthesized in moderate to high yields including the crystal structure of 6g (Scheme 3). While the presence of an alkenyl group led to oxazinone 6d with this substitution in position 4, the products with alkyl groups in position 4 or 5 or an alkenyl group in position 5 did not form. Also, products 6 with the difluoromethyl or ethoxycarbonyl groups in position 2 did not form.

Table 1 Optimization of the reaction conditions leading to cyclopenta[c]isoquinolines 2a and 3a from 5-acylated triazole 1a

Entry	Time (min)	Additive	Ratio <b>2a/3a</b> <sup>a</sup>	<b>2a</b> Yield <sup><math>b</math></sup> (%)	$3a  ext{ Yield}^b (\%)$
1	120	_	48:52	n.d.	n.d.
2	60	KF	27:73	12	23
3	60	$AlF_3$	37:63	n.d.	n.d.
4	60	CsF	42:58	n.d.	n.d.
5	60	AgF	78:22	42	10
6	60	NaF	54:46	n.d.	n.d.
7	60	$FeF_3$	38:62	n.d.	n.d.
8	30	$CuF_2$	84:16	41	12
9	30	$KF^c$	13:87	Traces	31

<sup>&</sup>lt;sup>a 19</sup>F NMR ratio. <sup>b</sup> Isolated yield. n.d. not determined. <sup>c</sup> With added NaOH (3 equiv.).

Scheme 2 Scope of products of the microwave-assisted transformation of 5-acyl-N-pentafluoroethylated 1,2,3-triazoles 1 (0.1–0.2 mmol) to cyclopenta[c]isoquinolines 2 and 3 or indeno[1,2-c]-isoquinolines 4.  $^a$ 2.11 mmol scale.  $^b$ Using KF (1.1 equiv.) and NaOH (3 equiv.) instead of CuF<sub>2</sub>.

Scheme 3 Scope of products of the microwave-assisted transformation of 5-acyl-*N*-pentafluoroethyl-1,2,3-triazoles 1 (0.1–0.25 mmol) to trifluoromethylated 6,6-difluoro-1,3-oxazines 5 and 1,3-oxazin-6-ones 6. <sup>a</sup>195 °C, 120 min.

# Conclusions

In conclusion, thermal denitrogenation of N-penta-fluoroethylated 4-substituted-5-acyl-1,2,3-triazoles in the presence of copper(II) fluoride affords depending on the nature of 5-acyl substitution 1-trifluoromethylcyclopenta[c]-isoquinolines, indeno[1,2-c]-isoquinolines, 2-trifluoromethyl-6,6-difluoro-1,3-oxazines, or products of their hydrolysis 2-trifluoromethyl-1,3-oxazin-6-ones. All these compounds result from the formation of ketenimine intermediates which undergo either 1,3-fluorine shift,  $S_E$ Ar and  $S_N$ Ar sequence, or 1,3-aryl shift, 1,5-fluorine shift, cyclization and another 1,5-fluorine shift sequence. The

Table 2 Optimization of the reaction conditions leading to 6,6-difluoro-1,3-oxazine 5a and 1,3-oxazinone 6a

4f, 56%

Entry	CuF <sub>2</sub> (equiv.)	Reaction time (min)	Ratio 5a/6a <sup>a</sup>	5a Yield $^b$ (%)	<b>6a</b> Yield $^b$ (%)
1	0	20	78:22	28	n.d.
2	0	5	92:8	60	n.d.
3	1.1	10	8:92	n.d.	39
4	1.1	20	1:99	n.d.	85

 $<sup>^{</sup>a}$  <sup>19</sup>F NMR ratio.  $^{b}$  Isolated yield. n.d. not determined.

presented methodology showcases advanced cyclization of ketenimine intermediates generated from triazoles and their application in the C–C bond formation for the synthesis of new heterocyclic structures.

# Data availability

The data supporting this article have been included as part of the ESI.†

### **Author contributions**

PB supervised the project. LJ contributed to experiments and product characterization. BK solved the crystal structures. LJ and PB jointly conceived the project, prepared the manuscript, and contributed to discussions.

### Conflicts of interest

There are no conflicts to declare.

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### References

- 1 D. B. Khadka, Q. M. Le, S. H. Yang, H. T. M. Van, T. N. Le, S. H. Cho, Y. Kwon, K. T. Lee, E. S. Lee and W. J. Cho, Design, Synthesis and Docking Study of 5-Amino Substituted Indeno[1,2-c]Isoquinolines as Novel Topoisomerase i Inhibitors, *Biochem. Mol. Med.*, 2011, 19, 1924–1929.
- 2 P. Song, P. Yu, J. S. Lin, Y. Li, N. Y. Yang and X. Y. Liu, Transition-Metal-Free β-C-H Bond Carbonylation of Enamides or Amides with a Trifluoromethyl Group as CO Surrogate for the Synthesis of 1,3-Oxazin-6-Ones, *Org. Lett.*, 2017, **19**, 1330–1333.
- 3 B. Y. Lalaev, O. A. Petina, N. N. Kuz'mich, I. P. Yakovlev, G. M. Alekseeva and V. E. Zakhs, Potentiometric Study on Acid Properties of Some 4-Hydroxy-6H-1,3-Oxazin-6- Ones. Structure-Biological Activity Relationship, *Russ. J. Gen. Chem.*, 2006, **76**, 645–648.
- 4 W. Yang, Z. Zhou, Y. Zhao, D. Luo, X. Luo, H. Luo, L. Cui and L. Li, Copper Catalyzed Inverse Electron Demand [4+2] Cycloaddition Fot the Synthesis of Oxazines, *Catalysts*, 2022, 12, 526.
- 5 N. Gupta, V. Saini, S. M. Basavarajaiah, M. O. Dar, R. Das and R. S. Dahiya, 1,3-Oxazine as a Promising Scaffold for the Development of Biologically Active Lead Molecules, *ChemistrySelect*, 2023, **8**, 1–18.
- 6 M. A. Campo and R. C. Larock, Synthesis of Fluoren-9-Ones via of o-Halobiaryls, *Org. Lett.*, 2000, 3, 1999–2001.
- 7 J. Dusemund and E. Kröger, Ein 1,3-Indandion-Derivat Aus Phthalaldehyd, *Arch. Pharm.*, 1987, **320**, 617–620.

- 8 P. Halder, A. Iqubal, K. Mondal, N. Mukhopadhyay and P. Das, Carbonylative Transformations Using a DMAP-Based Pd-Catalyst through Ex Situ CO Generation, *J. Org. Chem.*, 2023, **88**, 15218–15236.
- 9 T. T. Pham, X. Chen, T. Söhnel, N. Yan and J. Sperry, Haber-Independent, Diversity-Oriented Synthesis of Nitrogen Compounds from Biorenewable Chitin, *Green Chem.*, 2020, 22, 1978–1984.
- 10 L. Janecký, A. Markos, B. Klepetářová and P. Beier, Lewis-Acid-Mediated Intramolecular Cyclization of 4-Aryl-5-Allyl-1,2,3-Triazoles to Substituted Cyclopentene Derivatives, *J. Org. Chem.*, 2023, 88, 1155–1167.
- 11 G. Cainelli, D. Giacomini, M. Gazzano, P. Galletti and A. Quintavalla, N-Acylation of 4-Alkylidene-b-Lactams: Unexpected Results, *Tetrahedron Lett.*, 2003, 44, 6269–6272.
- 12 Y. M. Zhu, W. Zhang, H. Li, X. P. Xu and S. J. Ji, Palladium Catalyzed Ring Expansion Reaction of Isoxazolones with Isocyanides: Synthesis of 1,3-Oxazin-6-One Derivatives, *Adv. Synth. Catal.*, 2021, 363, 808–818.
- 13 B. F. Risitano, G. Grassi, F. Foti, F. Caruso, G. L. Vecchio and V. T. Cannizzaro, Ring-Enlargemen of Isoxazol-5-Ones to 1,3-Oxazin-6-Ones, *J. Chem. Soc., Perkin Trans.*, 1979, 24, 1522– 1524.
- 14 E. M. Beccalli, T. Benincori and A. Marchesini, 1,3-Oxazin-6-Ones from 5(2H)-Isoxazolones, *Synthesis*, 1988, **8**, 630–631.
- 15 T. Matsuda, K. Yamanaka, Y. Tabata and T. Shiomi, Synthesis of Trisubstituted 1,3-Oxazin-6-Ones via Base-Catalyzed Ring-Opening Annulation of Cyclopropenones with N-(Pivaloyloxy)Amides, *Tetrahedron Lett.*, 2018, 59, 1458–1460.
- 16 O. A. Petina, I. P. Yakovlev and D. Geffken, Preparation of Arylpropynamides and Their Reaction with Malonyl Acid Derivatives, *Synthesis*, 2013, 45, 803–809.
- 17 J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001– 2011), Chem. Rev., 2014, 114, 2432–2506.
- 18 E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly and N. A. Meanwell, Applications of Fluorine in Medicinal Chemistry, *J. Med. Chem.*, 2015, **58**, 8315–8359.
- 19 K. Müller, C. Faeh and F. Diederich, Fluorine in pharmaceuticals: looking beyond intuition, *Science*, 2007, 317, 1881–1886.
- 20 Fluorine in Pharmaceutical and Medicinal Chemistry, ed. V. Gouverneur and K. Müller, Imperial College Press, Ondon, 2012.
- 21 Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai and N. Shibata, Current contributions of Organofluorine Compounds to the Agrochemical Industry, *iScience*, 2020, 23, 101467.
- 22 P. Jeschke, Recent developments in fluorine-containing pesticides, *Pest Manage. Sci.*, 2024, **80**, 3065–3087.
- 23 Q. Wang, H. Song and Q. Wang, Fluorine-containing agrochemicals in the last decade and approaches for fluorine incorporation, *Chin. Chem. Lett.*, 2022, 33, 626–642.

- 24 L. Janecký and P. Beier, Lewis Acid-Mediated Transformations of 5-Acyl-N-Fluoroalkyl-1,2,3-Triazoles to Cyclopentenones, Indenones, or Oxazoles, *RSC Adv.*, 2024, 14, 13640–13645.
- 25 Z. E. Blastik, S. Voltrová, V. Matoušek, B. Jurásek, D. W. Manley, B. Klepetářová and P. Beier, Azidoperfluoroalkanes: Synthesis and Application in Copper(I)-Catalyzed Azide–Alkyne Cycloaddition, *Angew. Chem., Int. Ed.*, 2017, 56, 346–349.
- 26 O. Bakhanovich and P. Beier, Synthesis, Stability and Reactivity of α-Fluorinated Azidoalkanes, *Chem.–Eur. J.*, 2020, **26**, 773–782.
- 27 A. Markos, V. Matoušek and P. Beier, Fluoroalkyl Azides and Triazoles: Unlocking a Novel Chemical Space, *Aldrichim Acta*, 2022, **55**, 37–44.
- 28 S. Voltrová, M. Muselli, J. Filgas, V. Matoušek, B. Klepetářová and P. Beier, Synthesis of Tetrafluoroethylene-and Tetrafluoroethyl-Containing Azides and Their 1,3-Dipolar Cycloaddition as Synthetic Application, *Org. Biomol. Chem.*, 2017, 15, 4962–4965.
- 29 E. Shaitanova, V. Matoušek, T. Herentin, M. Adamec, R. Matyáš, B. Klepetářová and P. Beier, Synthesis and Cycloaddition Reactions of 1-Azido-1,1,2,2-Tetrafluoroethane, *J. Org. Chem.*, 2023, 88, 14969–14977.
- 30 A. Markos, L. Janecký, T. Chvojka, T. Martinek, H. Martinez-Seara, B. Klepetářová and P. Beier, Haloalkenyl Imidoyl

- Halides as Multifacial Substrates in the Stereoselective Synthesis of N-Alkenyl Compounds, *Adv. Synth. Catal.*, 2021, **363**, 3258–3266.
- 31 A. Markos, S. Voltrová, V. Motornov, D. Tichý, B. Klepetářová and P. Beier, Stereoselective Synthesis of (Z)-β-Enamido Triflates and Fluorosulfonates from N-Fluoroalkylated Triazoles, *Chem.–Eur. J.*, 2019, **25**, 7640–7644.
- 32 A. Markos, L. Janecký, B. Klepetářová, R. Pohl and P. Beier, Stereoselective Synthesis of (Z)-β-Enamido Fluorides from N-Fluoroalkyl- And N-Sulfonyl-1,2,3-Triazoles, *Org. Lett.*, 2021, 23, 4224–4227.
- 33 A. Kubíčková, A. Markos, S. Voltrová, A. Marková, J. Filgas, B. Klepetářová, P. Slavíček and P. Beier, Aza-Wolff Rearrangement of N-Fluoroalkyl Triazoles to Ketenimines, Org. Chem. Front., 2023, 10, 3201–3206.
- 34 A. Kubíčková, S. Voltrová, A. Kleman, B. Klepetářová and P. Beier, One-Pot Multistep Synthesis of 1-Fluoroalkylisoquinolines and Fused Fluoroalkylpyridines from *N*-Fluoroalkyl-1,2,3-Triazoles, *Org. Chem. Front.*, 2024, 11, 4442–4448.
- 35 L. George, K. P. Netsch, G. Penn, G. Kollenz and C. Wentrup, Oxoketene-Oxoketene, Imidoylketene-Imidoylketene and Oxoketenimine- Imidoylketene Rearrangements. 1,3-Shifts of Phenyl Groups, Org. Biomol. Chem., 2006, 4, 558–564.