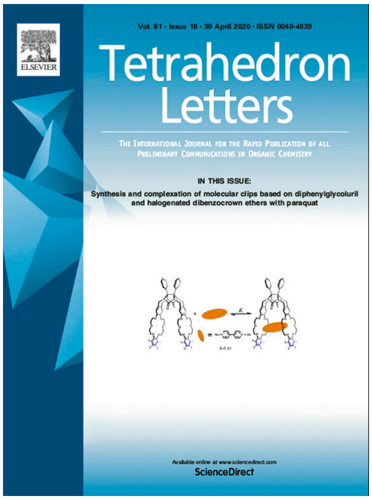

Dediazoniative Functionalization of Chromen-4-one and Chromen-2-one Diazonium-BF_4 Salts in BMIM-ILs. Direct Access to the -F, -I, -$OSO(CF_3)$=NTf, and -$N(Tf)_2$ Derivatives, and Facile Synthesis of Chromenone Azo-Dyes by Coupling to Activated Arenes

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PII: S0040-4039(20)30639-0
DOI: https://doi.org/10.1016/j.tetlet.2020.152179
Reference: TETL 152179

To appear in: *Tetrahedron Letters*

Received Date: 10 June 2020
Accepted Date: 25 June 2020

Please cite this article as: Gutierrez, L.F., Agemura, Y., Laali, K.K., Dediazoniative Functionalization of Chromen-4-one and Chromen-2-one Diazonium-BF_4 Salts in BMIM-ILs. Direct Access to the -F, -I, -$OSO(CF_3)$=NTf, and -$N(Tf)_2$ Derivatives, and Facile Synthesis of Chromenone Azo-Dyes by Coupling to Activated Arenes, *Tetrahedron Letters* (2020), doi: https://doi.org/10.1016/j.tetlet.2020.152179

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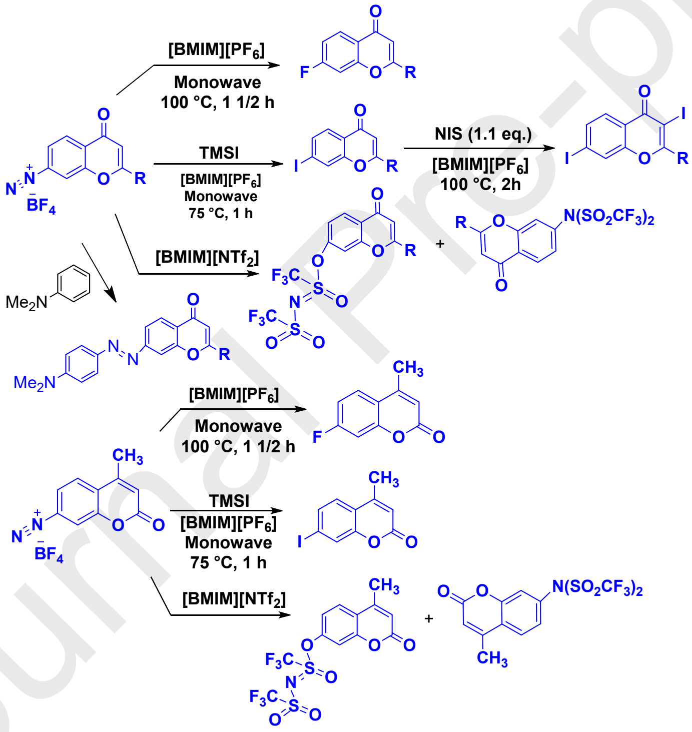
Graphical Abstract



Abstract

Chromenone-diazonium-BF_4 salts were isolated as stable powders by diazotization of the 7-amino-derivatives with $NaNO_2/HBF_4$. The 7-Fluoro-derivatives were synthesized by fluorodediazoniation in [BMIM][PF_6], while the 7-iodo-derivatives were obtained by iodadediazoniation with TMSI/[BMIM][PF_6]. Further iodination with NIS furnished the 2,7-di-iodo derivative. Dediazoniation in [BMIM][Tf_2N] gave the corresponding chromenone-$OSO(CF_3)=NTf$ compounds as major products, along with chromenone-$N(Tf)_2$ and the 7-fluoro-derivatives. Chromenone-diazonium salts undergo facile diazo-coupling with isomeric trimethoxybenzenes and dimethylaniline at r.t in aqueous EtOH or in [BMIM][PF_6] to give azo-dyes.

Keywords

Chromenone diazonium salts; fluorodediazoniation; iododediazoniation; chromenone-OSO(CF_3)=NTf and chromenone-NTf_2; diazo-coupling

Highlights

Synthesis of stable chromenone diazonium salts

IL-mediated halo-functionalization of chromenones

Direct access to iodo- and fluoro-chromenones

Synthesis of chromenone azo-dyes

Chromen-4-one and its 2-phenyl-derivative (flavone), and chromen-2-one (coumarin) constitute highly significant structural motifs that are present in a broad range of natural products with diverse biological activities.[1,2] As privileged building blocks with antitumor, antioxidant, anti-inflammatory, and antimicrobial activity, they are widely employed in medicinal chemistry and drug development.[3-6] In addition, the coumarin moiety has been adopted in the design of small-molecule fluorescent chemosensors.[7]

Developing iodo-functionalization approaches for chromenones is important since these compounds can then be further functionalized by metal-mediated coupling methodologies. Interest in fluoro-functionalization stems from possible application of the fluorinated derivatives in drug development. The 3-iodo-chromones have been synthesized by cyclization of 2-methoxyarylalkynones and suitably functionalized chalcones,[8,9] and by a number of other methods that involve multistep operations and those that suffer from poor regioselectivity.[9] Synthesis of difluorinated chromenones were reported by cyclization/fluorination of ortho-hydroxyaryl-enaminone using Selectfluor,[10] and synthesis of some hydroxyl-fluoro-amino-chromenones was realized by a multicomponent reaction that employed NFSI.[11]

In connection to our previous studies on dediazoniative functionalization of arenes in BMIM-ILs,[12-16] we report here facile methods for halo-functionalization of substituted chromenones via dediazoniative functionalization of their diazonium-BF_4 salts in BMIM-ILs, and for the synthesis of their azo-dyes by coupling to activated arenes.

Chromenone diazonium salts **1a**-**3a** were synthesized by diazotization of their commercially available 7-amino-precursors with $NaNO_2/HBF_4$ and isolated as stable salts in 85% to 74% yields after purification (Figure 1).

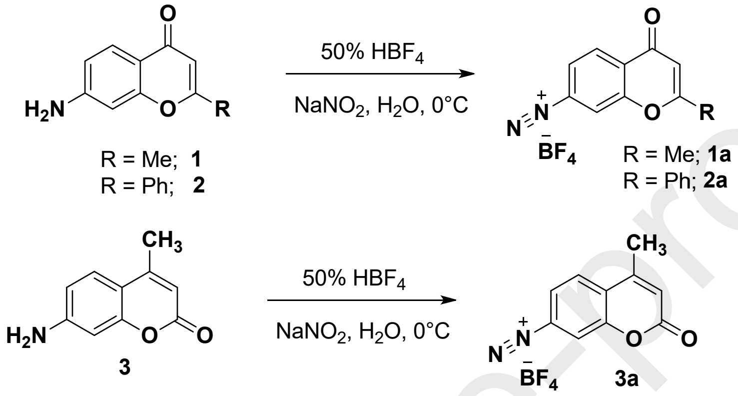


Figure 1. Stable chromenone-diazonium-BF_4 salts

The 7-fluoro-chromenones **1b-3b** were synthesized by fluorodediazoniation in [BMIM][PF_6] (Figure 2) in yields ranging from 50% to 40% by heating in a Monowave reactor[17] or in a conventional oil bath.

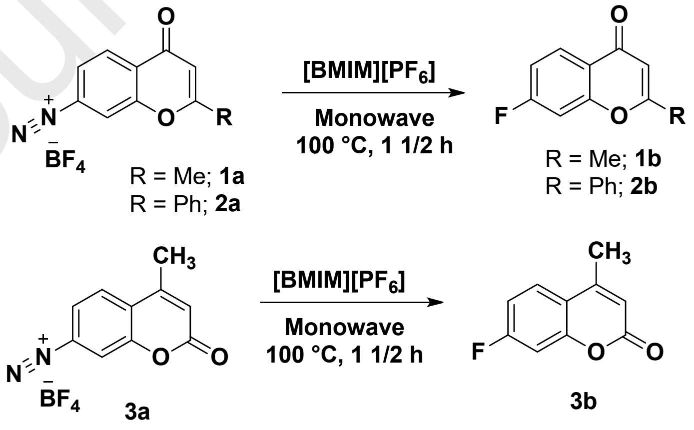


Figure 2. Facile access to the 7-Fluoro-derivatives

Focusing on iodo-functionalization, the 7-iodo-chromenones **1c-3c** (Figure 3) were obtained by reaction with TMSI in [BMIM][PF_6], in isolated yields ranging from 75% to 57% after purification. Subsequently, the 3,7-diiodo-derivative **1d** was successfully obtained by further iodination of **1c** with NIS in [BMIM][PF_6].[18] Attempted direct di-iodination with NIS in BMIM-IL starting with the diazonium salts **1a-2a** gave mixtures from which the di-iodo compounds **1d-2d** could not be isolated cleanly.

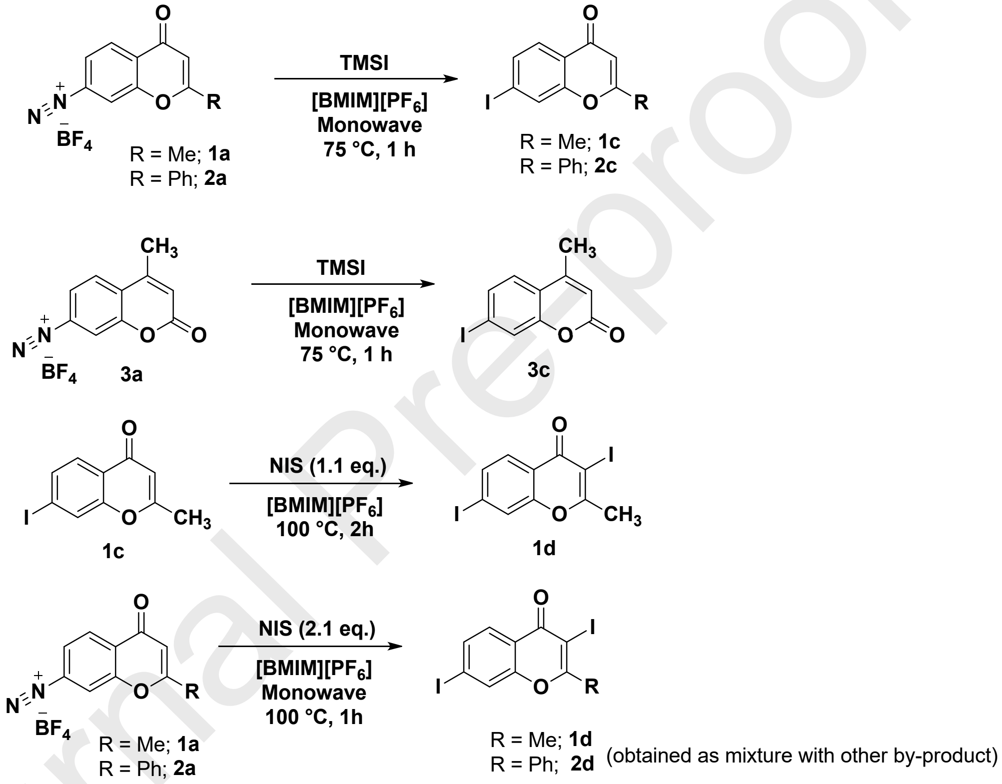


Figure 3. Synthesis of the iodo-chromenones

We have previously shown that substituted benzenediazonium-BF_4 salts undergo metathesis in [BMIM][NTf_2] and upon thermal or photolytic dediazoniation produce the N-(trifluoromethylsulfonyl)aryloxytrifluoromethylsulfoximines as major products, along with Ar-$N(Tf)_2$ and Ar-F.[14,15] This method provides direct access to trifluoromethylated derivatives whose syntheses are otherwise quite challenging. Since the efficacy of this protocol for fluorofunctionalization of heterocyclic diazonium salts was an open question, we explored this method in the present study to introduce these fluoro-substituents into chromenones. Thus thermal dediazoniation of **1a-3a** in [BMIM][NTf_2] produced the novel chromenonesulfoximines **1e-3e**, in a mixture with the 7-fluoro-derivatives **1b-3b**, along with minor amounts of the N-triflamides **1f-3f** (Figure 4). Product ratios, as determined by ^{19}F NMR, demonstrate that despite the "non-nucleophilic" nature of [NTf$_2$] it can compete effectively with fluoride anion to capture the heteroaryl cations derived from chromenone-diazonium salts, but its relative effectiveness decreases in going from **1a** to **3a**, and this in turn could provide an additional route for harvesting more of the corresponding 7-F derivatives (**1b-3b**).

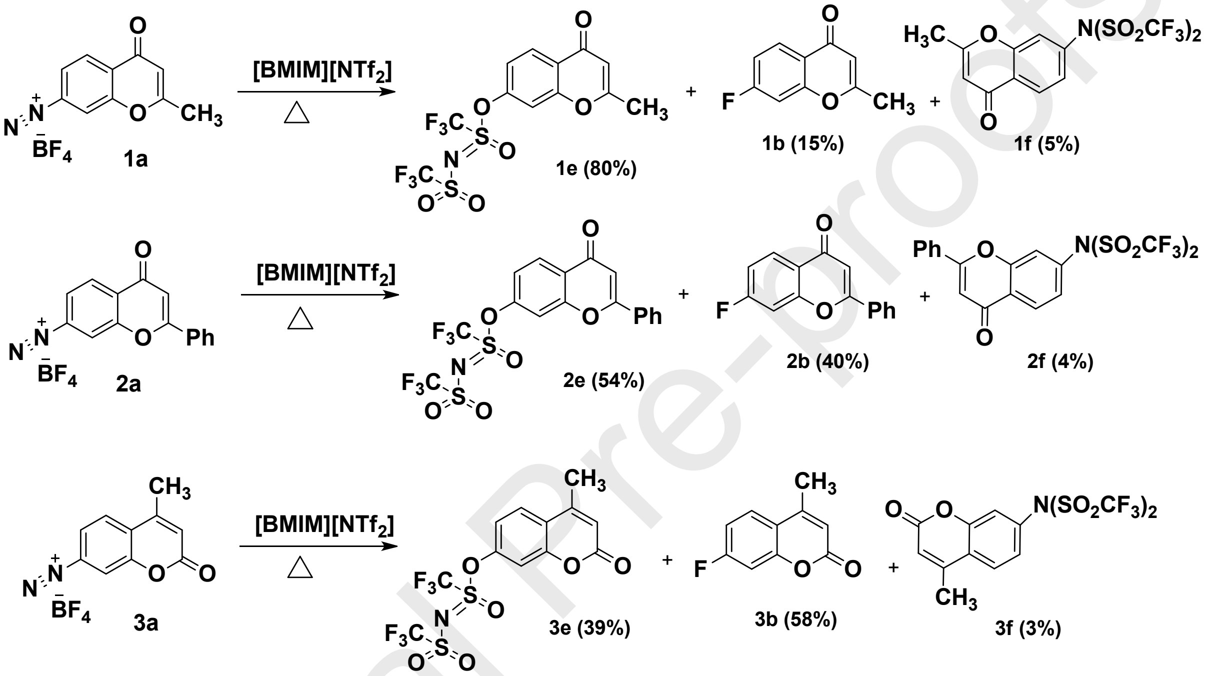
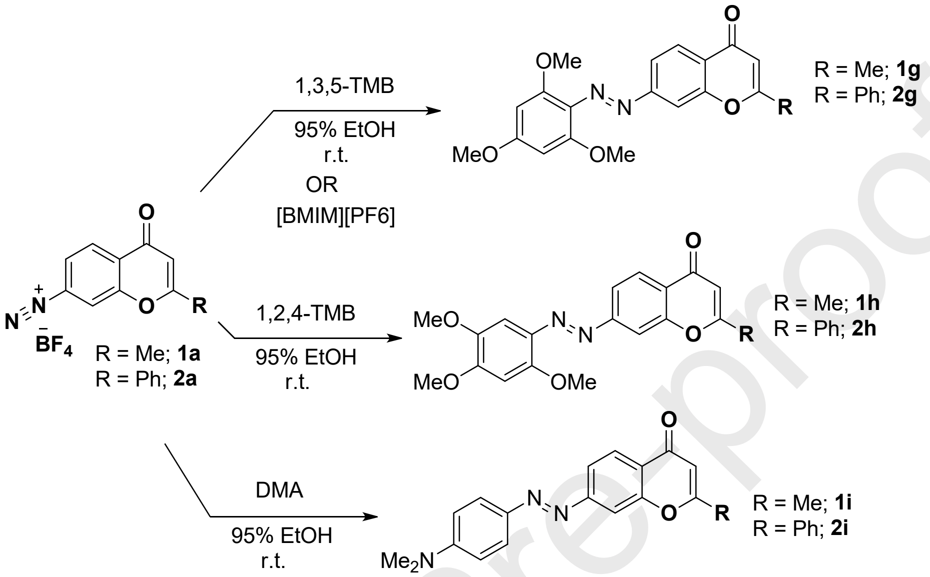


Figure 4. Dediazoniation products in [BMIM][NTf$_2$]

Coumarin-containing azo-dyes have attracted attention for their favorable photophysical properties. These compounds are typically synthesized by using coumarin or a coumarin-bearing moiety as nucleophile which is coupled to an activated PhN_2^+ salt.[19] Examples in which the coumarin moiety is the electrophilic partner reacting with activated nucleophiles to form azo-dye appear to be quite rare.[20]

In the present study, chromenone-diazonium salts **1a** and **2a** reacted with isomeric trimethoxybenzenes (TMB) and dimethylaniline (DMA) in EtOH solvent at r.t. to give the corresponding azo-dyes (Figure 5). Isolated yields for coupling to TMB were in 79% to 60% range. Lower yields were obtained in coupling with DMA due to isolation difficulties and solubility issues. Azo-coupling of **1a** and **2a** with 1,3,5-TMB was also performed in BMIM-IL as solvent, but extraction/isolation issues were more challenging. The color of chromenone-bearing azo-dyes range from dark red to orange, depending on the coupling component. Considering the ongoing interest in the optical properties of coumarin-dyes,[18-19] the presently described simple method could help increase the diversity of chromenone-based azo-dyes for photophysical studies.



In summary, the efficacy of IL-mediated halo-dediazoniation protocols for direct access to iodinated and fluorinated chromenones is demonstrated. Coupling of chromenone-diazonium salts to activated arenes provides a straightforward method to access new chromenone-bearing azo-dyes.

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Supporting Information

Experimental procedures and analytical data for this article are gathered in the supplemental information file along with NMR spectra.

Declaration of interest: None

Acknowledgements

K.L. thanks University of North Florida for the Outstanding Faculty Scholarship and Presidential Professorship awards, Faculty scholarship and UNF Foundation Board grants, and the Dean's Leadership Council award.

Declaration of Interest Statement

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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