Regioselective Synthesis of 3-Haloalkyl-isoxazoles from the Electrophilic Cyclization of Halogenated Oximes

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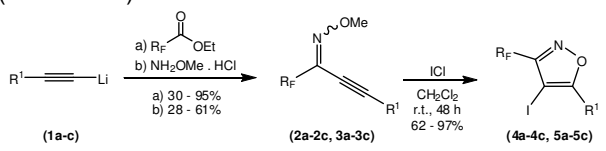
INTRODUCTION

Heterocycles constitute a major group of organic compounds. Among the great variety of existing heterocycles, the isoxazole core stands out due to its synthetic versatility and broad spectrum of interesting biological activities.[1] Additionally, the development of new strategies for synthesizing halogenated heterocycles has received much attention since the presence of such groups is often associated with improvements in pharmacological properties of organic molecules.[2] From a synthetic perspective, the regio and stereoselective control for the introduction of haloalkyl substituents in heterocycles is limited. Therefore, efficient and simple methods for the straightforward synthesis of haloalkyl-isoxazoles are highly desired.

RESULTS AND DISCUSSION

Several studies showed that the electrophilic cyclization of substituted acetylenes can be an efficient way to generate many heterocycles, including isoxazoles.[3] These results prompted us to evaluate such approach for the synthesis of a series of new 5-alkyl(phenyl)-3-haloalkyl-4-iodo-isoxazoles **(4a-4c, 5a-5c)** from the electrophilic cyclization of halogenated 2-alkyn-1-one *O*-methyl oximes **(2a-2c, 2a-2c)**. The procedure involves: *(a)* preparation of the ynones, (*b)* synthesis of the *O*-methyl oximes, and *(c)* electrophilic cyclization (Scheme 1).



Compd.	R^1
1a	Ph
1b	C_4H_9
1c	C_5H_{11}

Compd.	R^1	R_F
2a, 4a	Ph	CF_3
3a, 5a	Ph	CCl_3
2b, 4b	C_4H_9	CF_3
3b, 5b	C_4H_9	CCl_3
2c, 4c	C_5H_{11}	CF_3
3c, 5c	C_5H_{11}	CCl_3

Scheme 1.

Some *O*-methyl oximes **(2a-2c, 2a-2c)** were isolated as a diastereoisomeric mixture. Two factors seem to be influencing this diastereoisomeric ratio: the R^1 bulkiness relative to the alkyne moiety and the electron withdrawing character of R_F. In our studies, the desired *E* isomer was always the predominant product.

The *O*-methyl oximes cyclization was conducted directly from the diastereosiomeric mixture and ICl was selected as the electrophile due to its remarkable performance in previous publications.[3] The (Z)-*O*-methyl oximes were easily separated from the isoxazoles after cyclization from crystallization or by column chromatography on silica gel.

CONCLUSION

Our studies has shown that the synthesis of 5-alkyl(phenyl)-3-haloalkyl-4-iodo-isoxazoles from the electrophilic cyclization of halogenated (*E*)-4-alkyl(phenyl)-1,1,1-trihalomethyl-3-in-2-one-*O*-methyloximes with ICl is very efficient and regioselective. In addition, since the isolated heterocycles are highly substituted they can be further modified in order to improve the molecule proprieties.

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REFERENCES

[1] (a) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles – Structure, Reactions, Synthesis, and Applications*, Willey-VHC Verlag GmbH and Co. KGaA, 2ª ed. **2003**. (b) Taldone, T.; Sun, W.; Chiosis, G, *Bioorg. Med. Chem.* **2009**, *17*, 2225.

[2] Taldone, T.; Sun, W.; Chiosis, G, *Bioorg. Med. Chem.* **2009**, *17*, 2225.

[3] (a) Waldo, J. P.; Larock, R. C. *Org. Lett.* **2005**, *23*, 5203. (b) Chen, Y.; Cho, C.-H.; Larock, R. C. *Org. Lett.* **2009**, *11*, 173.