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Organoallylaluminum reagents promote easy access to trihalomethyl triazolyl homoallylic alcohols analogous to rufinamide

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ABSTRACT

The results of allylation reactions employing allylaluminum reagents are described for 5-substituted (2,6-difluorobenzyl)-4-trifluoro(chloro)acetyl-1*H*-1,2,3-triazoles (**1**), in which the 5-substituents are H, Me, and Ph. The allylating reagents were generated in situ by the catalytic insertion of aluminum into allyl and crotyl bromides (**2**), in order to furnish a new series of twelve trihalomethyl triazolyl homoallylic alcohols (**3**) at yields of up to 94%. The excellent reactivity of these organoallyl reagents is highlighted as an economical alternative to the indium-mediated reactions to produce homoallylic alcohols, which are important building blocks in organic synthesis.

The direct construction of carbon skeletons containing functional groups capable of being transformed in adjacent steps has a growing importance in organic synthesis. Among the several ways to perform it, the γ-insertion of allylic organometallic nucleophiles into carbonyl compounds is one of the most remarkable tools found in the literature.[1] The homoallylic alcohols obtained from these reactions are highly featured in synthetic procedures for building many biologically active molecules such as macrolides, polyhydroxylated natural products, and polyether antibiotics.[2]

Although indium-mediated allylation reactions have become very popular, mainly due to the possibility of performing Barbier procedures in aqueous media,[3] the high cost of this metal makes the process expensive. In this context, aluminum is a metal that has several attractive features such as low toxicity, low cost, and tolerance of a wide number of important functional groups, due to the low ionic character of the carbon–aluminum bond.[4] Unfortunately, the direct insertion of aluminum into organohalides is difficult, due to the presence of an oxidized layer covering the metal surface, being the proper activation required to occur the reaction.[5]

As an alternative, in 2002, Takai and Ikawa described the preparation of allylaluminum reagents under very mild conditions, employing indium metal as the catalyst.[6]

Upon searching the literature, we found that most of the studies of allylation reactions involve aldehydes or simple ketones.

Recently, our research group described the synthesis of 5-alkyl(aryl)-1-(2,6-difluorobenzyl)-4-trihaloacetyl-1*H*-1,2,3-triazoles.[7] These heterocycles, which have a triazole core and a trihalomethyl group like many substances with high applicability in various branches of the pharmacological and agricultural fields, are analogous structures of Rufinamide, a commercial drug employed for the treatment of Lennox–Gaustaut syndrome, which is a severe form of epilepsy.

Thus, in view of the importance of the molecules afore mentioned, as well as few examples of allylation reactions involving trihalomethyl ketones found in the literature, in this work we wish to disclose the chemical behavior of these trifluoro(chloro)acetyl-1*H*-1,2,3-triazoles (**1a–f**) in allylation reactions, by employing an inexpensive procedure in order to obtain a series of trihalomethyl triazolyl homoallylic alcohols (**3a–l**). We also wish to compare the effect of the fluorine, chlorine, and hydrogen atoms of the CX_3 groups (Scheme 1). As a starting point for the study, we investigated the Barbier procedure, described by Preite et al.[8] for inserting allyl bromide into triazole **1a**. Unfortunately, for this method, a long reaction time was required to obtain the desired homoallylic alcohol. This suggests that, in this case, the aluminum only acts as a reducing agent, and the indium is responsible for the conversion. This supposition is anchored in the high oxophilicity of the organoalluminun reagents, which show low stability when exposed to air—conditions employed in Preite's method. After this disappointing result, we decided to replace the

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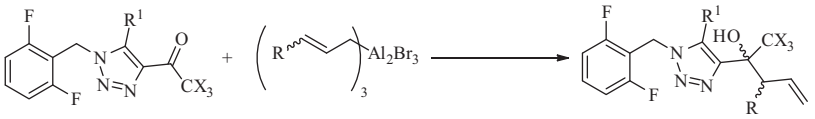


1a-f **2a-b** **3a-l**

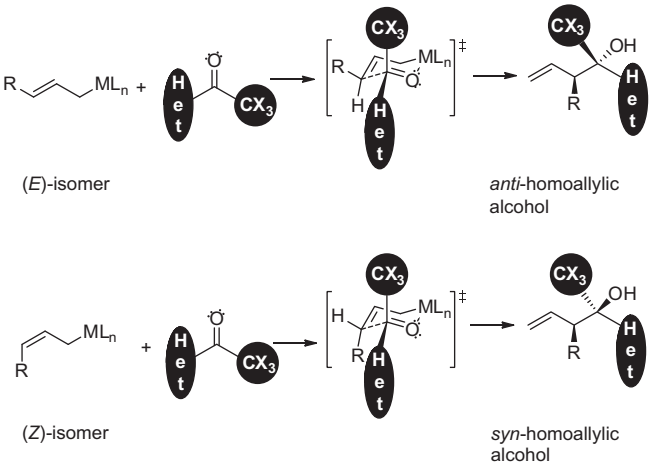
Scheme 1. Addition of the allyl and crotyl aluminum to trihaloacetyl ketones (**1a–f**).

reaction methodology with an improvement of Takai's method, disclosed by Knochel et al.[9]

Thus, under argon atmosphere, the allyl bromide was reacted with aluminum flakes and In^0 in anhydrous THF, at 0 °C for 1 h. The corresponding allylic aluminum reagent (**2a**) was obtained with a conversion rate of up to 90% (determined by GC–MS from iodolyzed aliquots). For the less reactive (*E*)-crotyl bromide, 2 h were necessary to obtain the crotyl aluminum (**2b**) at a similar rate of conversion. In the next step, the solution containing the respective organometallic reagent was added to each trihaloacetyl ketone solution (**1a–f**) in anhydrous THF and an argon atmosphere that had been previously cooled to −78 °C, and then stirred at this temperature for 2 h.[12] The results from these reactions are summarized in Table 1.

Although the yields were good, the compounds derived from (*E*)-crotyl bromide (**3g–l**) still showed low diastereoselectivity. Explanations in the literature rely on the fact that the addition of allylic nucleophiles, which have small groups at the γ positions, to carbonyl compounds, occurs via a six-membered chair-like transition state (Zimmerman–Traxler transition state model).[10] This configuration, which is responsible for the very high stereodifferentiation level, that is, normally observed for these reactions, implies that anti-homoallylic alcohol is obtained when the (*E*)-allylic nucleophile is employed, while the (*Z*)-allylic nucleophile provides a *syn*-homoallylic alcohol (Scheme 2).

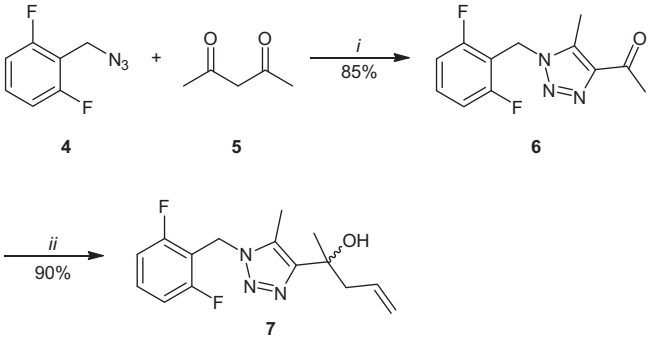
Additionally, other studies show that, even starting from (*E*)-allyl halides, the allylic organometallics generated in situ by a reductive process can be in equilibrium between the two possible species, and the most thermodynamic *trans*-isomer is at the highest concentration.[11] Thus, due to the low energy barrier necessary for the metallotropic rearrangement of the crotyl aluminum to occur, even performing the organometallic synthesis in an ice bath was not enough to prevent the equilibration of allyl aluminum reagents. On the other hand, when lower temperatures were applied,



(*E*)-isomer *anti*-homoallylic alcohol

(*Z*)-isomer *syn*-homoallylic alcohol

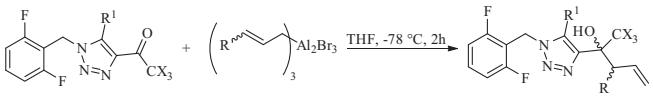
Scheme 2. Plausible reaction mechanism.



4 **5** **6** **7**

Scheme 3. Synthesis of the compounds **6** and **7**.[13] Reagents and conditions: *i* = K_2CO_3, EtOH, reflux, 24 h; *ii* = **2a**, THF, −78 °C, 2 h.

Table 1
Yields and melting points for the new trihalomethyl triazolyl homoallylic alcohols (**3a–l**)



Compound	R	R^1	X	Mp (°C)	Yield[a] (%)
3a	H	H	F	75–76	90
3b	H	Me	F	78–80	94
3c	H	Ph	F	123–124	91
3d	H	H	Cl	143–144	88
3e	H	Me	Cl	131–133	92
3f	H	Ph	Cl	171–173	94
3g	Me	H	F	85–87	89
3h	Me	Me	F	65–66	86
3i	Me	Ph	F	103–105	90
3j	Me	H	Cl	116–118	85
3k	Me	Me	Cl	118–120	90
3l	Me	Ph	Cl	190–191	91

[a] The compounds derived from crotyl bromide (**3g–l**) were attained as a mixture of two diastereoisomers in the proportion of 70:30 (determined by ^{1}H NMR).

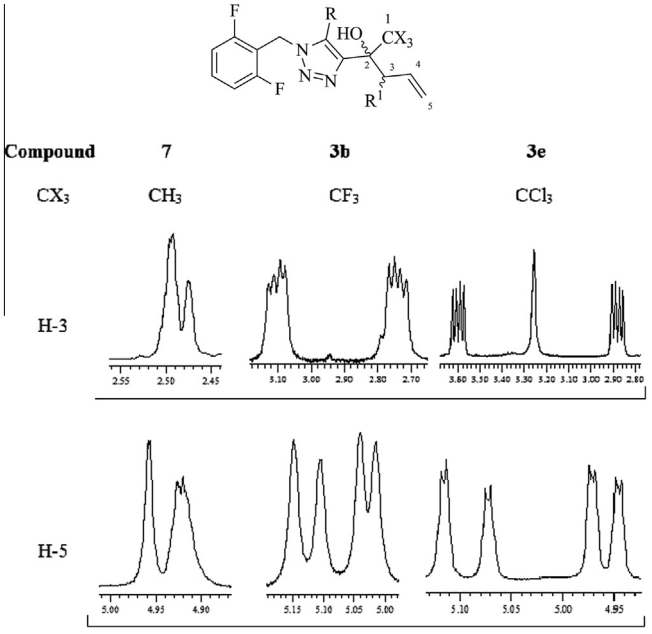


Figure 1. Influence of the CX_3 in the H-3 and H-5 chemical shifts.

low concentrations of organometallics were observed, even after long reaction times.

An interesting characteristic observed for the compounds **3a–f** was the influence of the CX_3 group at the chemical shift of the allylic moiety hydrogens, mainly at both H-5, located six bonds away from the fluorines and chlorine atoms. In the substituted trichoromethyl compounds, the sets of signals corresponding to these hydrogens appear to be more separated than in the substituted trifluoromethyl. In order to compare this effect, we performed the synthesis of the hydrogenated analog (**7**) for the compounds **3b** and **3e** (Scheme 3).

Comparing the results of the NMR ^1H analyses, it is possible to recognize that, although the fluorine is the most electronegative among the three atoms, the highest shift separation was observed for the chlorine-substituted molecules. This fact suggests that the larger the steric size of the CX_3 group, the more rigid the conformation adopted by the molecule. The preferred conformation appears to place the hydrogen atoms closer to the hydroxyl group, and this is reflected in the difference in the chemical shifts (Fig. 1).

In summary, we have reported the efficient preparation of trihalomethyl triazolyl homoallylic alcohols from the addition of allylic aluminum reagents to trihaloacetyl groups. This economical protocol, although showing limitations for allyl halides substituted with small groups, was able to furnish the desired compounds at considerable yields and under very mild conditions.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.02.091.

References and notes

1. Yamamoto, H.; Oshima, K. *Main Group Metals in Organic Synthesis*; Wiley-VCH: Weinheim, 2004.
2. (a) Nicolaou, K. C.; Kim, D. W.; Baati, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3701; (b) Nicolaou, K. C.; Ninkovic, S.; Sarabia, F.; Vourloumis, D.; He, Y.; Valllberg, H.; Finlay, M. R. V.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 7974; (c) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3; (d) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569; (e) Germay, O.; Kumar, N.; Thomas, E. J. *Tetrahedron Lett.* **2001**, *42*, 4969; (f) Romo, D.; Meyer, S. D.; Johnson, D. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 9345.
3. Li, C. J. *Chem. Rev.* **2005**, *105*, 3095.
4. (a) Negishi, E.-i.; Takahashi, T.; Baba, S.; Van Horn, D. E.; Okukado, N. *J. Am. Chem. Soc.* **1987**, *109*, 2393; (b) Negishi, E.-i. *Acc. Chem. Res.* **1982**, *15*, 340; (c) Ku, S.-L.; Hui, X.-P.; Chen, C.-A.; Kuo, Y.-Y.; Gau, H.-M. *Chem. Commun.* **2007**, 3847; (d) Zweifel, G.; Miller, J. A. In *Inorganic Reactions*; Dauben, W. G., Ed.; Wiley: New York, 1984.
5. (a) Rieke, R. D. *Top. Curr. Chem.* **1975**, *59*, 1; (b) Rieke, R. D. *Aldrichimica Acta* **2000**, *33*, 52.
6. Takai, K.; Ikawa, Y. *Org. Lett.* **2002**, *4*, 1727.
7. Bonacorso, H. G.; Moraes, M. C.; Wiethan, C. W.; Luz, F. M.; Meyer, A. R.; Zanatta, N.; Martins, M. A. P. *J. Fluorine Chem.* **2013**, *156*, 112.
8. Preite, M. D.; Geroldi, H. A. J.; Carvajal, A. P. *ARKIVOC* **2011**, *vii*, 380.
9. Peng, Z.; Blümke, T. D.; Mayer, P.; Knochel, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 8516.
10. (a) Mejuch, T.; Gilboa, N.; Gayon, E.; Wang, H.; Houk, K. N.; Marek, I. *Acc. Chem. Res.* **2013**, *46*(7), 1659; (b) Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655.
11. (a) Roush, W. R. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon: Oxford, 1990; Vol. 2, (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207; (c) Kennedy, J. W. J.; Hall, D. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4732; (d) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763.
12. *General procedure for preparation of trihalomethyl triazolyl homoallylic alcohols (**3a–l**) and (**7**):* Aluminum flakes (3 mmol–0.081 g) and In (0.1 mmol–0.011 g) were placed in a 50 ml Schlenk flask and dried under vacuum (1 mbar) for 5 min with a heat gun. After returning to room temperature, the system was backfilled with argon and a solution of allylic bromide (1.5 mmol) in anhydrous THF (5 mL) was added. The reaction mixture was stirred at 0 °C for 1 h for the allyl bromide and 2 h for the crotyl bromide. The resulting solution was then quickly added to a glass flask containing a solution of the respective triazole 1 (1.0 mmol) in anhydrous THF (3 mL) at −78 °C and in an argon atmosphere. The resulting mixture was stirred in these conditions for 2 h. The reaction was then quenched with 5 ml of aqueous HCl solution (10% v/v) and the mixture was extracted with ether (3 × 20 mL). The combined extracts were washed with brine (3 × 15 mL), dried over Na_2CO_3, and then concentrated in vacuum. The crude products 3 and 7 were purified by column chromatography, employing silica gel as the stationary phase and hexane/EtOAc 1:1 (v/v) as the eluent. The products were attained as white powders in all cases. Data for *2-(1-(2,6-difluorobenzyl)-1H-1,2,3-triazolo-4-yl)-1,1,1-trifluoropent-4-en-2-ol* (**3a**): Please see the atoms numbering for NMR data at the supporting information: ^1H NMR (400 MHz, DMSO-d_6, 25 °C) δ = 8.13 (s, 1H, H-9), 7.51 (tt, $^4J_{H-F}$ = 6.8 Hz, $^3J_{H-H}$ = 8.3 Hz, 1H, H-4), 7.16–7.20 (m, 2H, H-3, H-5), 6.72 (s, 1H, OH), 5.70 (s, 2H, H-7), 5.60 (ddt, $^3J_{H-H}$ = 16.9 Hz, $^3J_{H-H}$ = 10.0 Hz, $^3J_{H-H}$ = 6.80 Hz, 1H, H-12), 5.08 (dd, $^3J_{H-H}$ = 17.4 Hz, $^3J_{H-H}$ = 1.7 Hz, 1H, H-13a), 5.00 (dd, $^3J_{H-H}$ = 10.2 Hz, $^3J_{H-H}$ = 1.7 Hz, 1H, H-13b), 2.94 (dd, $^2J_{H-H}$ = 14.3 Hz, $^3J_{H-H}$ = 7.2 Hz, 1H, H-11a), 2.76 (dd, $^2J_{H-H}$ = 14.3 Hz, $^3J_{H-H}$ = 7.2 Hz, 1H, H-11b). ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) δ = 160.5 (dd, $^1J_{C-F}$ = 250 Hz, $^3J_{C-F}$ = 7 Hz, C-2, C-6); 144.9 (s, C-8), 131.4 (t, $^3J_{C-F}$ = 10 Hz, C-4), 130.9 (s, C-12), 125,0 (q, $^1J_{C-F}$ = 287 Hz, CF3), 124.3 (s, C-9), 118.7 (s, C-13), 111.5 (dd, $^2J_{C-F}$ = 19 Hz, $^4J_{C-F}$ = 6 Hz, C-3, C-5), 110.9 (t, $^2J_{C-F}$ = 19 Hz, C-1), 72.9 (q, $^2J_{C-F}$ = 28 Hz, C-10), 40.7 (t, $^3J_{C-F}$ = 4 Hz, C-7), 37.9 (s, C-11). GC–MS (EI, 70 eV): *m/z* (%) 333 (M+, 23), 316 (10), 292 (47), 264 (10), 127 (100), 101 (12). Anal. Calcd. for $C_{14}H_{12}F_5N_3O$ (333): C, 50.46; H, 3.63; N, 12.61. Found: C, 50.43; H, 3.62; N, 12.51.
13. *Procedure for preparation of 4-acetyl-1-(2,6-difluorobenzyl)-5-methyl-1H-1,2,3 triazole (**6**):* Sodium carbonate (10 mmol) was added to a solution of 2,6-difluorobenzyl azide (5 mmol) and acetylacetone (5 mmol) in ethanol (10 ml). The reaction mixture was stirred under reflux for 24 h. Subsequently, distilled water (10 mL) was added and the solution was neutralized with aqueous HCl (30% v/v). The organic fraction was extracted with diethyl ether and dried with anhydrous sodium sulfate. The organic fraction was extracted with diethyl ether, dried with anhydrous sodium sulfate, and then concentrated under a rotary evaporator to yield the crude product. The crude product was purified by column chromatography, employing silica gel as the stationary phase and hexane/EtOAc as the eluent, to give a white solid.