Flash generation of α-(trifluoromethyl)vinyllithium and application to continuous flow three-component synthesis of α-trifluoromethylamides.

Author(s)
Nagaki, Aiichiro; Tokuoka, Shinya; Yoshida, Jun-ichi

Citation
Chemical communications (2014), 50(95): 15079-15081

Issue Date
2014-10-21

URL
http://hdl.handle.net/2433/198580

Type
Journal Article

Textversion
author
Flash Generation of \( \alpha \)-(Trifluoromethyl)vinyllithium and an Application to Continuous Flow Three-Component Synthesis of \( \alpha \)-Trifluoromethylamides†

Aiichiro Nagaki,a Shinya Tokuoka,a and Jun-ichi Yoshida*a

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

\( \alpha \)-(Trifluoromethyl)vinyllithium was generated and used for the reaction with electrophiles at \(-78^\circ C\) in a flow microreactor although the batch reaction should be carried out at ca. \(-100^\circ C\), and the method was applied to continuous flow three-component synthesis of \( \alpha \)-trifluoromethylamides.

Trifluoromethyl-substituted vinylmetals\(^1\) such as \( \alpha \)-(trifluoromethyl)vinyllithium serve as powerful building blocks\(^2\) for constructing CF\(_3\)-containing molecules.\(^3\) However, because \( \alpha \)-(trifluoromethyl)vinyllithium is very unstable,\(^4\) it should be generated and reacted at extremely low temperatures if we use batch macro reactors. In fact, Tarrant\(^4\) and Ichikawa\(^2\) reported independently that the generation of \( \alpha \)-(trifluoromethyl)vinyllithium followed by the reaction with an electrophile should be carried out at ca. \(-100^\circ C\) because of rapid elimination of LiF to give 1,1-difluoroallene. Notably, batch reactions are often carried out using an excess amount of \( \alpha \)-(trifluoromethyl)vinyllithium, and the yields are usually reported based on the amounts of electrophiles. Here, we show that flash chemistry\(^5\,6\) using flow microreactor systems\(^7\,8\,9\) enables the generation and reactions of \( \alpha \)-(trifluoromethyl)vinyllithium at more easily accessible temperatures to give the desired products in good yields without using an excess amount of the lithium reagent. We also report here that the method enables continuous flow three-component synthesis\(^10\,11\,12\) of \( \alpha \)-trifluoromethylamides,\(^13\) which serve as fascinating motifs in peptidomimetics.

A flow microreactor system consisting of three T-shaped micromixers (M\(_1\), M\(_2\) and M\(_3\)) and three microtube reactors (R\(_1\), R\(_2\) and R\(_3\)) shown in Figure 1 was used for Br/Li exchange of 2-bromo-3,3,3-trifluoropropene with \( s \)-BuLi to generate \( \alpha \)-(trifluoromethyl)vinyllithium followed by reactions with electrophiles.

First, we examined the reaction using benzaldehyde as an electrophile, and the desired product was obtained in a good yield (79%) based on 2-bromo-3,3,3-trifluoropropene at \(-78^\circ C\) (Table 1). The reactions with other aldehydes also gave the corresponding products in good yields as shown in Table 1. Thus, the flash method enables efficient generation and use of \( \alpha \)-(trifluoromethyl)vinyllithium at easily accessible conditions.

![Fig. 1](image_url)
The reactions with isocyanates are interesting. Quenching with methanol gave the compounds having a methoxy group, although the use of acetic acid as a quenching agent gave the desired alkenes having CF3 and amide groups in good yields (Table 1).

The formation of the compounds having a methoxy group can be explained by deprotonation of methanol by the initially formed lithium amide followed by the addition of the methoxide ion to the carbon-carbon double bond activated by the electron withdrawing CF3 and amide groups. This explanation leads to the idea of using carbon nucleophiles having an acidic proton instead of the Br/Li exchange of 2-bromo-3,3,3-trifluoropropene, the 25°C reaction of the resulting carbamion (Nu-Li+) adds to the electron-deficient carbon-carbon double bond. Protonation gives the corresponding three-component coupling products.

We chose to use malonate esters as carbon nucleophiles. Thus, the Br/Li exchange of 2-bromo-3,3,3-trifluoropropene, the reaction of the resulting α-(trifluoromethyl)vinyl lithium with an isocyanate, and the subsequent reaction with a malonate ester were integrated14 using a flow microreactor system consisting of four T-shaped micromixers (M1, M2, M3 and M4) and four microtube reactors (R1, R2, R3 and R4) shown in Figure 3.

As shown in Table 2, the integration of the reactions was successfully achieved with diethyl malonate, dibenzyl malonate, and di-tert-butyl malonate to obtain the corresponding addition products in good yields, although the use of 1,3-diketones such as 2,4-pentanedione did not give the desired products.

In conclusion, flash chemistry enables efficient generation of α-(trifluoromethyl)vinyl lithium and its reactions with electrophiles at –78°C. Space integration of reactions enabled three-component synthesis of α-trifluoromethylamides by successive reactions of α-(trifluoromethyl)vinyl lithium with isocyanates and malonate esters. The key to the success of the three-component coupling is deprotonation of malonate esters by the lithium amide intermediates followed by the nucleophilic attack of the resulting carbanion on the carbon-carbon double bond activated by the CF3 and the amide groups. This mode of reaction integration adds a new dimension to continuous flow multicomponent coupling.15 Further applications of the present method to the continuous-flow synthesis of fluorine-containing organic compounds16 are currently in progress in our laboratory.

Acknowledgements

This work was partially supported by the Grant-in-Aid for Scientific Research (S) (no. 26220804) and Scientific Research (B) (no. 26288049). We also thank Taiyo Nippon Sanso for providing a low temperature cooling device and partial financial support.

Notes and references


