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Journal of Fluorine Chemistry 125 (2004) 33–35
JOURNAL OF FLUORINE CHEMISTRY
www.elsevier.com/locate/jfluchem

Selective fluorination of an aryl triazolinone herbicide intermediate

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Received 11 September 2003; received in revised form 22 September 2003; accepted 24 September 2003

Dedicated to Professor R. Eric Banks on the occasion of his 70th birthday

Abstract

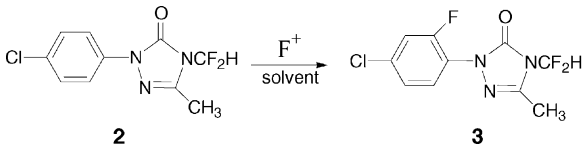
Fluoroaryl 1,2,4-triazolin-5-ones are an important class of herbicidal compounds useful in a variety of crop protection applications, primarily for the control of grassy and broad-leaf plant species. While a number of different synthetic strategies can be used for the step-wise preparation of these complex molecules, it is generally preferred to introduce fluorine later in the synthetic pathway, since the presence of fluorine and other halogens has a dominant effect on all subsequent synthetic steps. We have investigated the reactions that occur between aryl triazolinones and a variety of fluorination agents, including F_2/N_2, XeF_2, $(CF_3SO_2)_2NF$, Selectfluor®, $CF_2(OF)_2$, CF_3OF, CH_3COOF, and CF_3COOF, and have used this knowledge to develop several alternative high-yielding routes to fluoroaryl 1,2,4-triazolin-5-ones. The fluorine introduction strategy and experimental results for a representative example of this important class of compounds are discussed herein.

Keywords: Direct fluorination; Selective fluorination; Electrophilic fluorination; Fluorination of aryl triazolinone; Fluoroaryl triazolinone

1. Introduction

Fluoroaryl 1,2,4-triazolin-5-ones are an important class of herbicidal compounds useful in a variety of crop protection applications, primarily for the control of grassy and broad-leaf plant species [1,2]. While a number of different synthetic strategies can be used for the step-wise preparation of these complex molecules, it is generally recognized that introduction of fluorine later in the synthetic pathway is preferential, since the presence of fluorine and other halogens on the aryl ring has a dominant effect on all subsequent synthetic steps. For instance, in the synthesis of the popular herbicide Carfentrazone (**1**) (Fig. 1), it is well documented that fluorine introduction late in the synthetic pathway is beneficial in a number of respects. For instance, an important step in this process involves difluoromethylene protection of the 4-position of the triazolinone ring, and this protection step is much less efficient when the aryl ring contains fluorine at the ortho position when compared to the efficiency of the process when the aryl ring does not contain fluorine [3]. This is probably due to the deactivating effect that the fluorine has on the process. A second example of when the presence of an aryl fluorine impacts subsequent synthetic steps is in the formation of the triazolinone ring itself. It is recognized that triazolinone ring formation starting from the fluoro-aryl hydrazine is relatively slower and lower-yielding when compared to ring formation from the aryl hydrazine that does not contain fluorine [4].

Aryl ring fluorination of triazolinone (**2**) to give the fluoroaryl triazolinone (**3**) is ideally suited to an electrophilic process as indicated in Eq. (1). A fluorination strategy employing Selectfluor® has recently appeared in the patent literature (Eq. (1), F^+ = Selectfluor®) [5,6] wherein treatment of (**2**) with two equivalents of Selectfluor® in refluxing CH_3CN over 48 h resulted in a 78% conversion, and a 48% isolated yield of (**3**) was obtained.



2 **3** (1)

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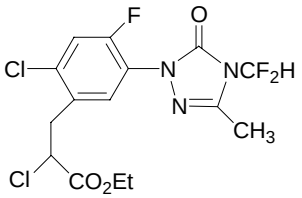
doi:10.1016/j.jfluchem.2003.09.002



Carfentrazone-Et (1)

Fig. 1.

In order to identify the most cost-effective fluorination route for commercial production of agrochemicals, and recognizing the potential applicability of a number of available electrophilic fluorination methodologies, we have investigated the reactions between aryl triazolinones and a variety of fluorination agents in an attempt to develop several alternative high-yielding routes to these fluoroaryl 1,2,4-triazolin-5-ones. The fluorine introduction strategy and experimental results are discussed in this paper.

2. Results and discussion

Aryl ring fluorination of triazolinone (**2**) is ideally suited to an electrophilic process since the aromatic ring is activated for substitution at the position ortho to the nitrogen heteroatoms. We have investigated the fluorination of triazolinone (**2**) according to Eq. (1) with a number of common electrophilic fluorination agents ($F^+ = F_2/N_2$, XeF_2, $(CF_3SO_2)_2NF$, Selectfluor®, $CF_2(OF)_2$, CF_3OF, $CH_3C(O)OF$, and $CF_3C(O)OF$) and the results are summarized in Table 1. The first entry in the table, representing Experiment 1, where treatment of the aryl triazolinone substrate with two equivalents of fluorine, delivered at 10% fluorine in nitrogen in acetonitrile solvent at −44 °C, resulted in 62% conversion of the starting material with 44% selectivity to the desired fluoroaryl triazolinone product (**3**).

This conversion is improved with the addition of three equivalents of F_2, together with 5% BF_3 etherate, which results in a conversion of 93% and a selectivity of 59% (Experiment 2). In Experiment 3, delivery of two equivalents of F_2 to a mixture of chloroform and trifluoroacetic acid containing **2**, in the presence of one equivalent of nitrobenzene as a radical scavenger, provides an improved conversion, but not an improvement in selectivity. Finally, Experiment 4 represents the best results achieved with F_2. In this experiment, a mixture of $CFCl_3$ and trifluoroacetic acid containing **2** was treated with two equivalents of F_2 at −48 °C, which resulted in near complete conversion of **2**, with 66% selectivity to product **3**.

The selectivity results using F_2 can be improved upon, in many cases, with the use of conventional electrophilic fluorination agents. Four representative examples are illustrated by Experiments 5–8 in Table 1. Thus, by using an equivalent of XeF_2, excellent selectivity to the desired product (**3**) is attained; however, the low conversion suggests that this reaction is quite sluggish.

In Experiments 6 and 7, improved conversions are observed using the powerful –OF fluorination agents trifluoroacetylhypofluorite and fluoroxytrifluoromethane. Finally, in Experiment 8, excellent results are attained by using the DesMarteau reagent, $(CF_3SO_2)_2NF$, in 1,2-DCE at refluxing conditions.

The best fluorination results observed in this study are illustrated in Experiments 9–11 using the powerful and selective fluorination agents acetyl hypofluorite and bis(-fluoroxy)difluoromethane.

Thus, in Experiment 9, using dilute concentrations of acetyl hypofluorite, CH_3COOF, in chloroform trifluoroacetic acid at −15 °C, 100% conversion of **2** is achieved, with very good selectivity (91%) to the desired product. In Experiment 10, using BDM, $CF_2(OF)_2$, complete conversion of **2** is also achieved; however, selectivity suffers a little

Table 1
Experimental conditions and results for the fluorination of compound **2** with various fluorination agents

Experiment	Fluorination agent	Solvent	Conversion (mol %)[a]	Selectivity (mol %)[a]
1	2 eq. 10% F_2 in N_2	CH_3CN at −44 °C	62	44
2	3 eq. 10% F_2 in N_2	CH_3CN at −44 °C, with 5% BF_3 etherate	93	59
3	2 eq. 10% F_2 in N_2	$CHCl_3/CF_3COOH$, 10:1 (v/v) at −39 °C, with 1 eq. nitrobenzene	100	58
4	2 eq. 10% F_2 in N_2	$CFCl_3/CF_3COOH$, 10:1 (v/v) at −48 °C	98	66
5	1 eq. XeF_2	CH_3CN at 0 °C, with 1% BF_3 etherate	3	100
6	1 eq. CF_3COOF	$CFCl_3/CF_3COOH$, 20:1 (v/v) at −49 °C	45	93
7	4.6 eq. CF_3OF (12% in N_2)	$CFCl_3/CF_3COOH$, 10:1 (v/v) at −12 °C	70	93
8	2 eq. $(CF_3SO_2)_2NF$	Refluxing 1,2-DCE/CF_3COOH	100	88
9	1.3 eq. CH_3COOF (1% in air)	$CHCl_3/CF_3COOH$, 3:1 (v/v) at −15 °C	100	91
10	1.4 eq. $CF_2(OF)_2$ (12% in N_2)	$CHCl_3/CF_3COOH$, 10:1 (v/v) at −45 °C	100	71
11	1.4 eq. $CF_2(OF)_2$ (12% in N_2)	$CHCl_3/CF_3COOH$, 10:1 (v/v) at −45 °C, with 1.4 eq. nitrobenzene	100	98

[a] Values determined by GC and NMR analysis of isolated product mixtures.

when compared to the prior result using acetyl hypofluorite. This is compensated for in Experiment 11, where the addition of a small amount of nitrobenzene acts as a radical scavenger, and results in complete conversion of **2** with very high selectivity to the desired product (**3**).

3. Summary

Because of the profound influence fluorine has on subsequent synthetic steps, aryl ring fluorination of aryl triazolinones is best achieved on the fully assembled aryl triazolinone and not earlier in the synthetic process. Using the specific example of the fluorination of compound **2**, we have demonstrated that a number of conventional electrophilic fluorination agents are effective for this purpose, and have achieved the best results, that being 100% conversion with 98% selectivity to the target molecule **3**, using BDM in the presence of a radical scavenger at low temperature in chloroform trifluoroacetic acid solvent.

4. Experimental

4.1. Starting materials

The starting aryl triazolinone substrate 2 was supplied by FMC Corporation and was used as received. All solvents were obtained from commercial sources and were used without purification. *Caution*: *Preparation and handling of the fluorination agents used in this work is potentially hazardous owing to the reactivity and unpredictable stability of some of these compounds. These fluorinating agents must only be prepared and used by experienced and fully trained personnel*. The fluorination agents were prepared by known literature methods: XeF_2 [7], $(CF_3SO_2)_2NF$ [8], Selectfluor® [9], $CF_2(OF)_2$ [10], CF_3OF [10], $CH_3C(O)OF$ [11], and $CF_3C(O)OF$ [12].

4.2. Experimental procedure—fluorination

All fluorination reactions were done in a 316-SS, 300-cc Parr Instrument Company stirred reactor, with the exception of reactions involving $(CF_3SO_2)_2NF$ and XeF_2 that were done in standard laboratory glassware.

In a typical fluorination experiment, the substrate **2** was loaded into the reactor together with the appropriate amount of solvent and reagent additive (if applicable). The reactor was then sealed, pressurized with dry N_2, and cooled to the appropriate reaction temperature (see Table 1). After attaining reaction temperature, F_2/N_2 or other fluorination agent was delivered to the stirred reaction mixture in the amount and at the rate noted in Table 1 for each experiment. When the fluorination was complete, the reactor and contents are purged with N_2 to ensure that all of the residual fluorination agent had been swept out and then warmed to room temperature and recovered from the reactor.

4.3. Experimental workup

The crude reaction mixture recovered is first evaporated to dryness on a Rotavap. The crude solid residue that remains is taken up into a minimum amount of acetone and then treated with saturated aqueous bicarbonate, $NaHCO_3$, until neutral. To the neutral solution is added enough water to affect complete precipitation of both **2** and **3** that are completely insoluble in water. The precipitated material is filtered and washed numerous times with water until it is a light yellow color. The filtered material can either be dried in vacuo or analyzed directly at this point. If desired, further purification can be accomplished using standard silica-gel chromatography and ethyl acetate:*n*-hexane (1:9 (v/v)).

4.4. 5-(4-Chloro-2-fluorophenyl)-2-difluoromethyl-3-methyltriazolinone *3*

Pale-yellow crystalline solid; ^1H (300.135 MHz, CD_3CN) δ (ppm): 7.3–7.6 ppm (3H, m, aromatic H-3, H-5, and H-6), 7.1 (1H, d, $J = 56$ Hz, C**H**F_2), 2.4 (3H, s, CH_3). ^{19}F (282.409 MHz, CD_3CN) δ (ppm): 100.7 (d, 2F, $J = 56$ Hz, C**F**$_2$H), −117.9 (m, 1F, $J = 12.2$ Hz, aromatic F). ^{13}C (75.469 MHz, CD_3CN) δ (ppm): 157.5 (d, $J = 272$ Hz, aromatic **C**–F), 109.2 (t, $J = 264$ Hz, **C**F_2H). EIMS 70 eV, *m/z* (rel. int.): 277 $[M]^+$ (47), 258 $[M - F]^+$ (2), 227 $[M - CF_2]^+$ (1), 184 $[M - C(O)NCF_2H]^+$ (9), 143 $[M - C(O)NCF_2HCCH_3N]$ (100).

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