



Nucleophilic difluoro(trimethylsilyl)methylation of arylidene Meldrum's acids



Alexander D. Volodin^{a,b}, Artem A. Zemtsov^a, Vitalij V. Levin^a, Marina I. Struchkova^a,
Alexander D. Dilman^{a,*}

^a N. D. Zelinsky Institute of Organic Chemistry, Leninsky prosp. 47, Moscow, 119991, Russian Federation

^b Higher Chemical College, Russian Academy of Sciences, Miusskaya sq 9, Moscow, 125047, Russian Federation

ARTICLE INFO

Article history:

Received 2 April 2015

Received in revised form 14 May 2015

Accepted 15 May 2015

Available online 28 May 2015

Keywords:

Arylidene Meldrum's acids

Conjugate addition

Organozinc reagents

Copper catalysis

ABSTRACT

A reaction of arylidene Meldrum's acids with difluoro(trimethylsilyl)methylzinc bromide in the presence of copper cyanide (10 mol%) is described. The primary addition products are hydrolyzed and decarboxylated followed by esterification of intermediate carboxylic acids affording β -Me₃SiCF₂-substituted esters. Protodesilylation of Me₃SiCF₂-group can be performed under mild conditions affording CHF₂-fragment.

© 2015 Elsevier B.V. All rights reserved.

1. Introduction

Nucleophilic fluoroalkylation reactions have emerged as a reliable tool for the introduction of fluorinated substituents into organic molecules [1]. While reactions of carbonyl compounds and azomethines are quite well developed [1], methods for addition to electron deficient alkenes are limited [2]. Within the last five years, a number of fluorinated zinc and copper organometallics have become available [3–6]. However, their reactions with Michael acceptors have not been described despite the fact that non-fluorinated organocopper species (with stoichiometric or catalytic amount of copper) are commonly used for conjugate addition [7]. Herein we demonstrate that *gem*-difluorinated reagent **1**, which is readily prepared by bromine/zinc exchange [3b] reacts with arylidene derivatives of Meldrum's acid under copper catalysis (Scheme 1).

2. Results and discussion

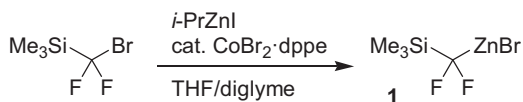
Compound **2a** obtained from *p*-anisaldehyde and Meldrum's acid, was selected as a model substrate and its reaction with reagent **1** (1.2 equiv) was evaluated (Table 1). The reaction

mixtures were analyzed by ¹⁹F NMR spectroscopy which allows the observation of primary addition product **3a** [8]. Virtually no reaction occurred in the absence of copper catalyst within 16 h at 0 °C along with significant decomposition (*ca.* 60%) of reagent **1**. In the presence of 10 mol% of copper cyanide the reaction proceeded slowly, but despite formation of adduct **3a** in 73% yield, the excess amount of organozinc reagent **1** was completely consumed, which may be ascribed to its decomposition. Subsequent optimization revealed that the reaction is best performed in the presence of dimethylformamide (DMF, 5 equiv) and benzyl triethylammonium chloride (1.2 equiv). DMF is believed to stabilize organometallic species but has a minor decelerating effect, while chloride ion increases the reaction rate.

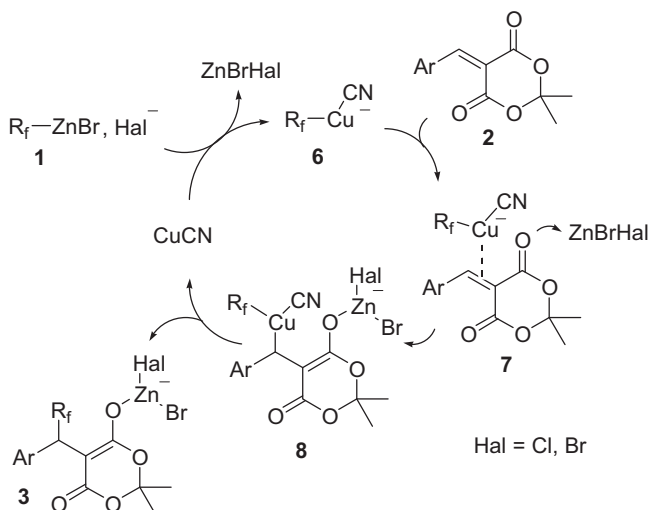
Under the optimized conditions, a variety of arylidene Meldrum's acids **2** were coupled with reagent **1** (Table 2). The reaction mixture was treated with hydrochloric acid to effect hydrolysis of Meldrum's acid moiety and decarboxylation affording acids **4**. Crude acids **4** were converted to esters **5** using methyl iodide/potassium carbonate system. In most cases, substrates **2** were converted to esters **5** in good yield, except for *ortho*-substituted compound **2g** and furaldehyde derivative **2j**, presumably because of their decreased reactivity.

Concerning the mechanism, we propose that the reaction starts from zinc/copper transmetalation generating organocopper species **6**, which forms *d*- π complex **7** (Scheme 2). Subsequent transformation of **7** into copper(III) intermediate **8** is believed to be the rate

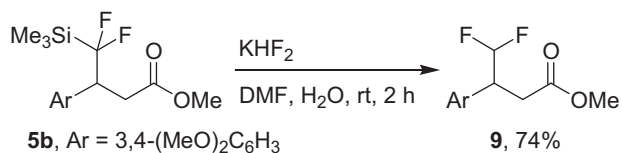
* Corresponding author. Tel.: +7 9104056988; fax: +7 4991355328.
E-mail addresses: adil25@mail.ru, dilman@ioc.ac.ru (A.D. Dilman).



Scheme 1. Preparation of reagent 1.



Scheme 2. Proposed mechanism.

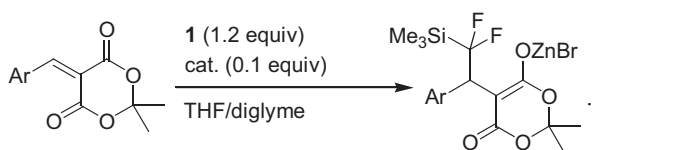


Scheme 3. Protodesilylation of ester 5b.

limiting step [9], and it is mediated by Lewis acidic zinc salt formed at the first step (or present in reagent 1 as a result of Schlenk equilibrium). Finally, reductive elimination from short-lived copper (III) species completes the catalytic cycle.

In esters 5, trimethylsilyl group could be readily replaced by hydrogen upon treatment with KHF_2 in DMF containing small amount of water, as exemplified by transformation of product 5b into ester 9. Therefore, the use of reagent 1 with subsequent protodesilylation corresponds to nucleophilic difluoromethylation of arylidene Meldrum's acids (Scheme 3).

Table 1
Reaction of substrate 2a

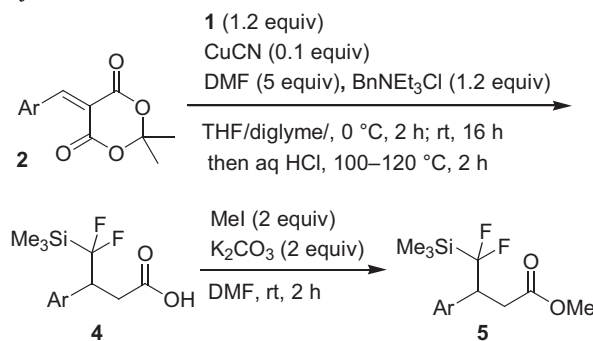
2a, Ar = 4-MeOC₆H₄

3a

Cat.	Additive (equiv)	Conditions	Yield of 3a, % ^a
–	–	0 °C, 16 h	<5
CuCN	–	0 °C, 16 h	73
CuCN	DMF (5)	0 °C, 2 h; rt 16 h	78
CuCN	DMF (5)	rt, 3 h	56
CuBr·SMe ₂	DMF (5)	0 °C, 2 h; rt 16 h	65
CuCN	DMF (5), BnNEt ₃ Cl (1.2)	0 °C, 2 h; rt 16 h	92

^a Determined by ¹⁹FNMR using PhCF₃ as internal standard.

Table 2
Synthesis of esters 5.



Substrate	Product	Yield of 5, % ^a
		92
		90
		74 ^b
		80
		75
		81
		55
		77
		82
		50

^a Isolated yield.

^b Methylation was performed using MeOH/H₂SO₄ system.

Download English Version:

<https://daneshyari.com/en/article/1313938>

Download Persian Version:

<https://daneshyari.com/article/1313938>

[Daneshyari.com](https://daneshyari.com)