HETEROCYCLES, Vol. 76, No. 1, 2008, pp. 215 - 219. © The Japan Institute of Heterocyclic Chemistry
Received, 22nd March, 2008, Accepted, 28th April, 2008, Published online, 1st May, 2008. COM-08-S(N)49

ONE STEP INTRODUCTION OF 4,4-BIS(TRIFLUOROACETYL)-1,3-BUTADIENE SYSTEM TO AROMATIC RINGS USING FLUORINE-CONTAINING 3,4-DIHYDRO-2*H*-PYRANS. A FACILE SYNTHETIC METHOD FOR 1,1,1,5,5,5-HEXAFLUORO-3-[(*E*)-3-ARYLALLYLIDENE]-PENTANE-2,4-DIONES

Norio Ota,[a] Etsuji Okada,[a]* Atsushi Sonoda,[a] Nobuyuki Muro,[a] Dai Shibata,[a] and Maurice Médebielle[b]

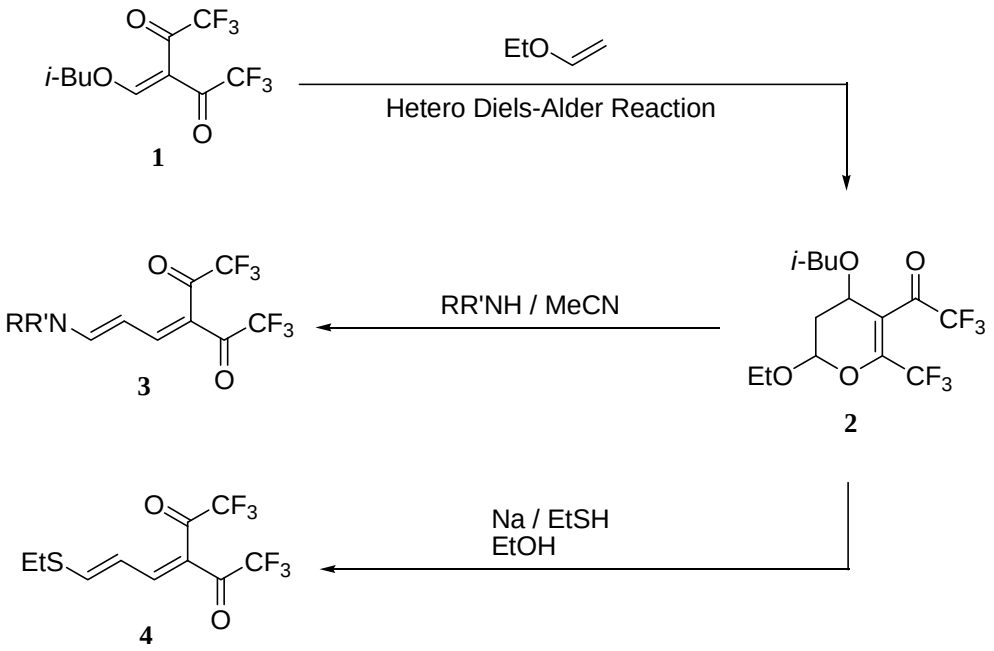
[a]Department of Chemical Science and Engineering, Graduate School of Engineering, Kobe University, Rokkodai-cho, Nada-ku, Kobe 657-8501, Japan Fax: +81(78)8036194; E-mail: okaetsu@kobe-u.ac.jp

[b]Université Claude Bernard Lyon 1 (UCBL), Institut de Chimie et Biochimie Moléculaires et Supramoléculaires (ICBMS), UMR CNRS-UCBL 5246, Laboratoire de Synthèse de Biomolécules, Bâtiment Chevreul, 5ème étage, 43 bd du 11 Novembre 1918, 69622 Villeurbanne Cedex, France

Abstract – New 1,1,1,5,5,5-hexafluoro-3-[(*E*)-3-arylallylidene]pentane-2,4-diones were synthesized in moderate to high yields by the ring-opening reaction of 1-(2-ethoxy-4-isobutoxy-6-trifluoromethyl-3,4-dihydro-2*H*-pyran-5-yl)-2,2,2-trifluoroethanone with aromatic compounds in refluxing trifluoroacetic acid.

The carbon-carbon bond formation has been one of the most significant and challenging subjects in organic chemistry. So, new methodologies for carbon-carbon bond forming reactions are of considerable interest in the field of organic synthesis.[1-3] On the other hand, 3-allylidenepentane-2,4-diones and 2-allylidenepropane-1,3-diones are valuable building blocks for the synthesis of various heterocycles. It has been reported that the reaction of 3-allylidenepentane-2,4-diones with hydroxylamine give isoxazole, isoxazolone and 1,2-oxazepine derivatives.[4] Moreover, the syntheses of 3*H*-[1,2]dithioles,[5] pyrazolines[6] and dihydrofurans[7] from various 2-allylidenemalonates have been reported. 2-(3-Amidoallylidene)malonates and 2-(3-aminoallylidene)malonates are also known to undergo intramolecular cyclization reaction to give the corresponding pyridines or pyridones.[8] Previously, we reported that the ring-opening reactions of

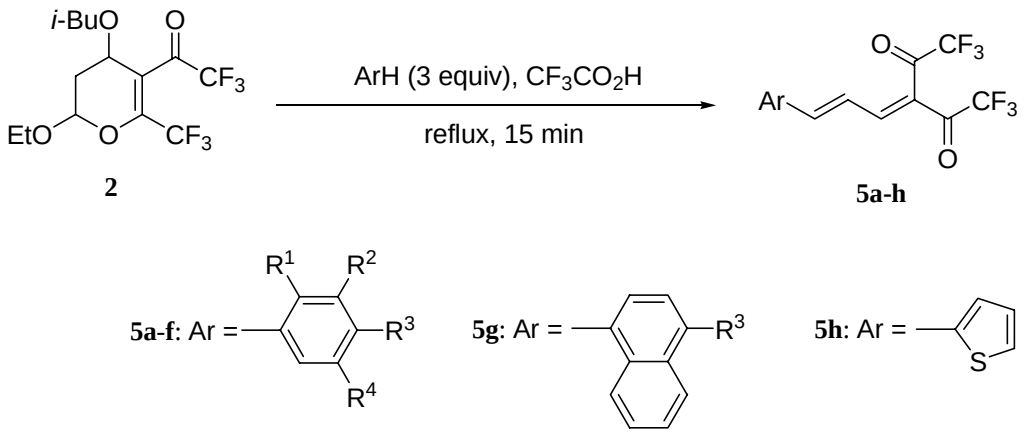
fluorine-containing dihydropyran derivative **2**, which was easily prepared by the hetero Diels-Alder reaction of bis(trifluoroacetyl)vinyl ethers **1** with ethyl vinyl ether,[9] with amines and sodium ethanethilolate afforded the corresponding 4,4-bis(trifluoroacetyl)-1,3-butadienylamines **3**[10] and 4,4-bis(trifluoroacetyl)-1,3-butadienyl ethyl sulfide **4**[11], respectively (Scheme 1).



Scheme 1

In this communication we wish to report a very facile and convenient synthetic method for 4,4-bis(trifluoroacetyl)-1,3-butadienylated aromatic compounds **5** through the acid-catalyzed C_8-unit introduction to aromatic rings by making use of fluorine-containing dihydropyran derivative **2**. Possibly, these new fluorinated 3-allylidenepentane-2,4-diones **5** can serve as versatile building blocks for the construction of *CF_3* -containing heterocycles, which may be expected to show interesting biological activities.[12-15]

The results of the present 4,4-bis(trifluoroacetyl)-1,3-butadienylation reaction of aromatics are shown in Scheme 2 and summarized in Table 1.[16] Reaction of **2** with monosubstituted benzenes, anisole (3 equiv.), easily proceeded in refluxing trifluoroacetic acid within 15 min to give **5a**, 4,4-bis(trifluoroacetyl)butadienylated only at the *p*-position, in 66% yield (entry 1). Thioanisole also exhibited almost the same reactivity with anisole to afford the desired **5b** in 55% yield (entry 2). Reaction of **2** with 1,3-disubstituted benzenes, for example, 1-methoxy-3-methylbenzene under the same conditions provided a mixture of two kinds of regioisomers **5c** (or **5c'**) and **5c'** (or **5c**) in 42% and 21% yields, respectively (entry 3). Separation of the mixtures into **5c** and **5c'** was easily performed by column chromatography. In contrast to this, 4,4-bis(trifluoroacetyl)butadienylation reactions with



Scheme 2

Table 1 Synthesis of 1,1,1,5,5,5-hexafluoro-3-[(*E*)-3-arylallylidene]pentane-2,4-diones (**5a-h**)

Entry	Compound	R^1	R^2	R^3	R^4	Product	Yield (%)[a]
1	**5a**	H	H	OMe	H	**5a**	66
2	**5b**	H	H	SMe	H	**5b**	55
3[b]	**5c**	OMe	H	Me	H	**5c** or **5c'**	42
	5c'	Me	H	OMe	H	**5c'** or **5c**	21
4[c]	**5d**	H	Me	OMe	H	**5d** or **5d'**	67
	5d'	H	OMe	Me	H		
5	**5e**	H	OMe	OMe	H	**5e**	72
6[c]	**5f**	Me	H	OMe	OMe	**5f** or **5f'**	89
	5f '	OMe	OMe	H	Me		
7	**5g**	-	-	OMe	-	**5g**	51
8	**5h**	-	-	-	-	**5h**	50

[a] Isolated yield.

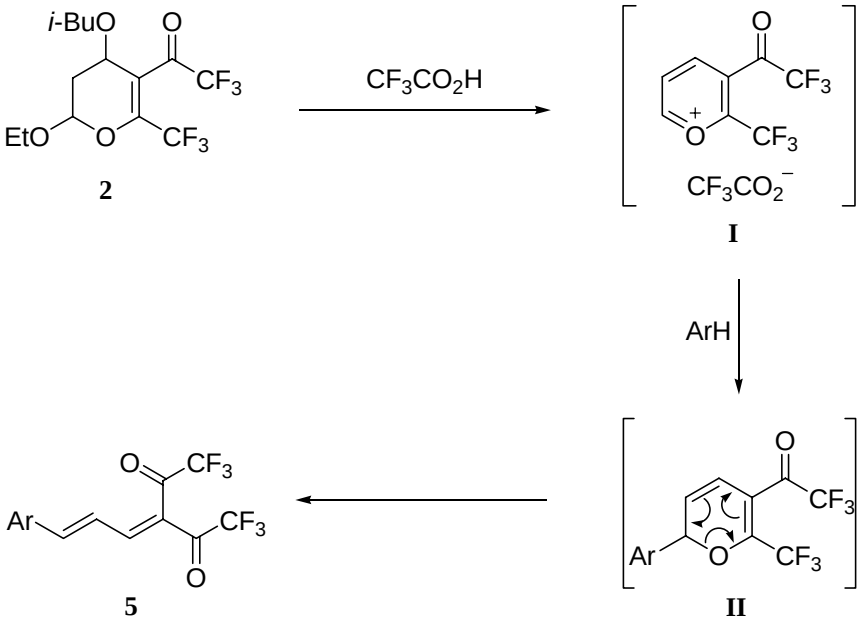
[b] Two kinds of regioisomers **5c** and **5c'** were formed and each of them was separated by column chromatography. The regiochemical structure was not determined.

[c] Either of regioisomers was formed and the regiochemical structure was not determined.

1,2-disubstituted benzenes such as 1-methoxy-2-methylbenzene and 1,2-dimethoxybenzene took place regioselectively to give the corresponding single isomers **5d** (or **5d'**) and **5e**, respectively, in good yields (entries 4 and 5). Similarly, trisubstituted benzenes, for example, 1,2-dimethoxy-4-methylbenzene reacted cleanly with **2** to afford the corresponding single regioisomer **5f** (or **5f'**) in 89% yield (entry 6). It was, moreover, found that this type of 4,4-bis(trifluoroacetyl)-1,3-butadienylation had application to other aromatic compounds, as 1-methoxynaphthalene (naphthalenes) and thiophene (heteroaromatics), to provide **5g** and **5h** in moderate yields (entries 7 and 8).

A possible pathway for the formation of **5** is depicted in Scheme 3. Elimination of alcohols from **2** by

trifluoroacetic acid occurs first to form pyrylium **I**, electrophilic substitution of aromatic compounds (ArH) with **I** gives 2*H*-pyran **II**, and finally **II** undergoes electrocyclic ring-opening reaction to afford **5**.



Scheme 3

The stereochemistry of all compounds **5a-h** was determined on the basis of ^{1}H-NMR spectral data. The large coupling constant $J_{CH=CH}$ (11-14 Hz) suggests the *E* configuration. The regiochemical structure on benzene ring of **5c**/**5c'**, **5d**/**5d'** and **5f**/**5f'** was not determined.

In conclusion, we have developed a very simple method for the introduction of fluorine-containing C_8-unit, 4,4-bis(trifluoroacetyl)-1,3-butadiene system, to aromatic rings and the novel fluorinated 3-(3-arylallylidene)pentane-2,4-diones **5**, which are not easily accessible by other methods, have been synthesized in one step by utilizing the acid-catalyzed ring-opening reaction of CF_3-containing dihydropyran derivative **2** with aromatics. Further work is under progress in our laboratory on the synthetic application of **5** to the fluorine-containing heterocycles of potentially biological importance.

REFERENCES AND NOTES

1. B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 259.
2. B. M. Trost, F. D. Toste, and A. B. Pinkerton, *Chem. Rev.*, 2001, **101**, 2067.
3. V. Ritleng, V. C. Sirlin, and M. Pfeffer, *Chem. Rev.*, 2002, **102**, 1731.
4. T. Kurihara, K. Nasu, Y. Mizuhara, and K. Hayashi, *Chem. Pharm. Bull.*, 1982, **30**, 2742; K. Huang, C. Li, Q. Liu, H. Bai, and Z. Mu, *Gaodeng Xuexiao Huaxue Xuebao*, 2004, **25**, 1264.
5. H. Quiniou and N. Lozac'h, *Bull. Soc. Chim. Fr.*, 1963, 1171.

6. H. Abdallah, R. Gree, and R. Carrie, *Can. J. Chem.*, 1985, **63**, 3031.
7. Z. Arnold, V. Kral, G. V. Kryshtal, and L. A. Yanovskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1983, 2162.
8. I. Shibuya and M. Kurabayashi, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 73; M. T. Cocco, C. Congiu, A. Maccioni, and A. J. Plumitallo, *Heterocycl. Chem.*, 1989, **26**, 1859.
9. M. Hojo, R. Masuda, and E. Okada, *Synthesis*, 1990, 347.
10. M. Hojo, R. Masuda, and E. Okada, *Synthesis*, 1990, 425.
11. M. Hojo, R. Masuda, and E. Okada, *Synthesis*, 1991, 46.
12. R. Filler and Y. Kobayashi, 'Biomedicinal Aspects of Fluorine Chemistry,' Kodansha & Elsevier Biomedical, Tokyo, 1982.
13. R. Filler, 'Organofluorine Chemicals and Their Industrial Applications,' Ellis Horwood, London, 1979.
14. J. T. Welch, *Tetrahedron*, 1987, **43**, 3123.
15. R. Filler, Y. Kobayashi, and L. M. Yagupolskii, 'Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications,' Elsevier, Amsterdam, 1993.
16. A typical experimental procedure for the synthesis of **5c** and **5c'**: To a mixture of **2**[9] (437 mg, 1.2 mmol) and 1-methoxy-3-methylbenzene (440 mg, 3.6 mmol) was added trifluoroacetic acid (2 mL) and this solution was stirred at reflux temperature for 15 min. The mixture was washed with 10% aq. Na_2CO_3 (30 mL) and H_2O (30 mL), extracted with CH_2Cl_2 (30 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude mixture was chromatographed on silica gel column using *n*-hexane/benzene (1:1) as eluent to give **5c** [yield: 184 mg (42 %)] and **5c'** [yield: 94 mg (21 %)]. **5c**: mp 58-59 °C (*n*-hexane/benzene); IR (KBr): $\nu_{C=O}$ = 1689 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.63 (d, 1H, *J* = 12.0 Hz, HC=C($COCF_3$)$_2$), 7.48 (d, 1H, *J* = 12.0 Hz, =CHAr), 6.88 (dd, 1H, *J* = 12.0, 12.0 Hz, -C<u>H</u>=CHAr), 6.67 (d, 1H, *J* = 6.4 Hz, H-6 in Ar), 6.63 (d, 1H, *J* = 6.4 Hz, H-5 in Ar), 6.58 (s, 1H, H-3 in Ar), 3.74 (s, 3H, OCH_3), 2.38 (s, 3H, CH_3); Anal. Calcd for $C_{16}H_{12}F_6O_3$: C, 52.47; H, 3.30; F, 31.12. Found: C, 52.47; H, 3.28; F, 31.26. **5c'**: mp 93-94 °C (*n*-hexane/benzene); IR (KBr): $\nu_{C=O}$ = 1682 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.64 (d, 1H, *J* = 12.0 Hz, HC＝C($COCF_3$)$_2$), 7.56 (d, 1H, *J* = 13.0 Hz, =CHAr), 7.23 (dd, 1H, *J* = 12.0, 13.0 Hz, -C<u>H</u>=CHAr), 7.23 (d, 1H, *J* = 8.0 Hz, H-6 in Ar), 6.66 (d, 1H, *J* = 8.0 Hz, H-5 in Ar), 6.59 (s, 1H, H-3 in Ar), 3.81 (s, 3H, OCH_3), 2.35 (s, 3H, CH_3); Anal. Calcd for $C_{16}H_{12}F_6O_3$: C, 52.47; H, 3.30; F, 31.12. Found: C, 52.52; H, 3.30; F, 31.42.