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A novel direct synthesis of (2,2-difluorovinyl)benzenes from aromatic aldehydes

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Abstract

A novel catalytic approach to (2,2-difluorovinyl)benzenes has been developed. It was found that hydrazones of aromatic aldehydes generated in situ could be converted to the corresponding (2,2-difluorovinyl)benzenes by catalytic olefination reaction (COR) with dibromodifluoromethane in the presence of CuCl.

Keywords: Difluoroalkenes; Dibromodifluoromethane; Catalysis; Copper; Carbonyl compounds; Olefination

1. Introduction

gem-Difluoroalkenes are very important fluorinated compounds, widely used in the synthesis of organofluoro compounds [1,2]. There are few methods for the preparation (2,2-difluorovinyl)benzenes, the most common is the Wittig-type condensation of carbonyl compounds with the difluoromethylene phosphorous ylides prepared from PPh_3 and CBr_2F_2 [2,3] or from PPh_3 and sodium chlorodifluoroacetate [3]. Also (2,2-difluorovinyl)benzenes can be prepared by palladium-catalyzed cross-coupling of aryl iodides or bromides with 2,2-difluorovinylzinc reagent [4], or by thermal decarboxylation of α,α-difluoro-β-lactones [5]. The necessity to use dry solvents, expensive and toxic reagents are significant disadvantages of these approaches.

2. Results and discussion

Earlier, we reported a novel catalytic olefination reaction (COR) of carbonyl compounds [6]. It was found that N-unsubstituted hydrazones of aldehydes and ketones are converted to olefins in high yields by treatment with polyhalogenalkanes in the presence of CuCl as catalyst. This methodology was successfully applied for the synthesis of a range of substituted alkenes [6–9]. We found that polyhalogenalkanes such as CCl_4 [6], $CHBr_3$ [7], CBr_4 [7], and CFCs, $CFCl_3$ [8], CF_3CCl_3 and $CF_2ClCFCl_2$ [9] can be used as C_1- or C_2-building blocks for the olefination of carbonyl compounds. The target halogen-containing alkenes were obtained in good yields. Remarkable features of the presented approach are availability of starting materials, mild reaction conditions, simplicity of reaction procedure and isolation of the products. Here we described a new *one-pot* synthesis of (2,2-difluorovinyl)benzenes from aromatic aldehydes **1a**–**h** using CBr_2F_2 as C_1-building block.

Previously, we found that two types of solvent and base systems may be used for synthesis of substituted alkenes in COR. Using DMSO and aqueous ammonia only traces of the desired difluoroalkene **3a** were obtained in the reaction of hydrazone of 4-chlorobenzaldehyde **2a** with CBr_2F_2. Main product of the reaction was the corresponding azine **4a** isolated in quantitative yield. Treatment of hydrazone **2a** with dibromodifluoromethane under modified reaction conditions (ethanol as solvent and 1,2-ethylenediamine as base) give 4-chloro-β,β-difluorostyrene **3a** in 35% yield. Using in situ generated hydrazone **2a** the target 1-chloro-4-(2,2-difluorovinyl)benzene **3a** was obtained in 36% yield (Scheme 1).

We investigated the reaction with a range of aromatic aldehydes under similar conditions and found that the

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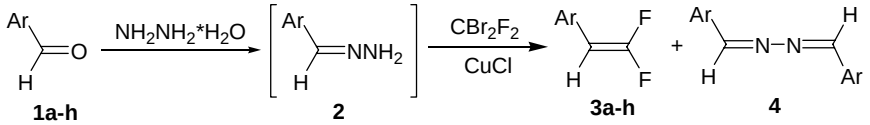
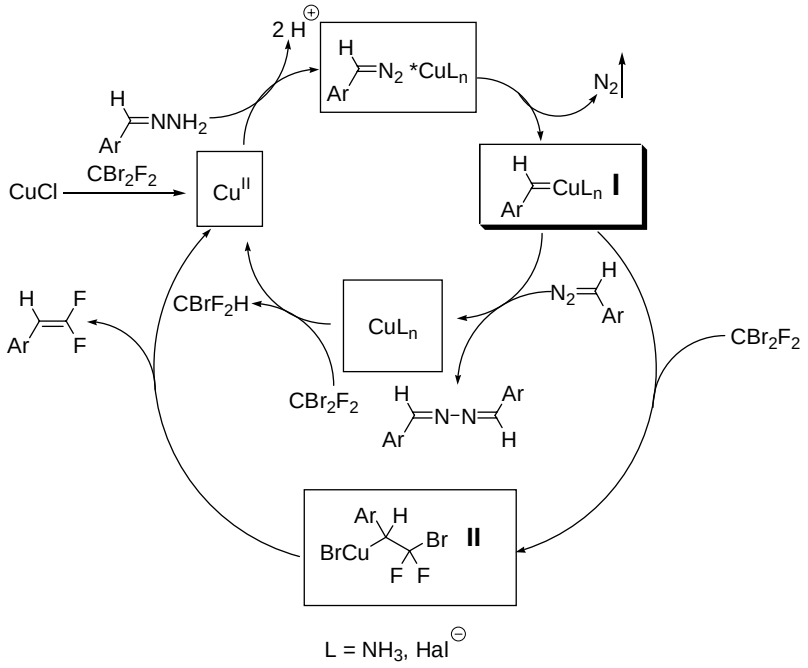


Scheme 1.

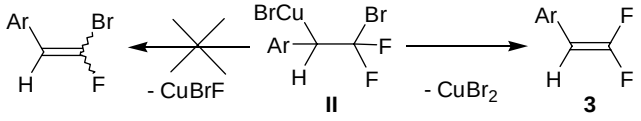


Scheme 2.

corresponding (2,2-difluorovinyl)benzenes **3a–g** were obtained in 20–36% yield (Table 1). Both aldehydes bearing electron withdrawing and electron-donating groups were converted into difluoroalkenes. In spite of moderate yields of target products the procedure is extremely simple and straightforward. It should be noted that the corresponding *sym*-azines were found to be the only by-products of the COR-process. In some cases azines **4a–c** were isolated, it was found that total yield of **3** and **4** was quantitative.

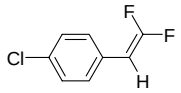
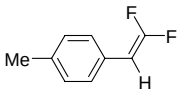
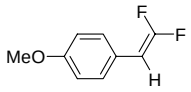
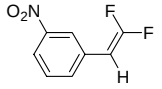
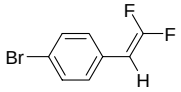
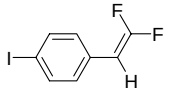
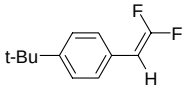
We found that reaction of hydrazones with CBr_2F_2 is in good agreement with the previously proposed general mechanism of this new catalytic olefination reaction [6–9]. At first step of catalytic cycle hydrazone **2** is oxidized by Cu(II) to give the corresponding diazoalkane (Scheme 2). Subsequent copper-catalyzed decomposition of diazoalkane leads to formation of copper–carbene complex **I**. Complex **I** is the key intermediate of the reaction [6,8]. Two routes for its subsequent transformation are possible. Complex **I** reacts with CBr_2F_2 to give the target (2,2-difluorovinyl)benzenes **3** and to regenerate the catalyst. This reaction proceeds via organocopper intermediate **II**. Another type of complex **I** transformation is its reaction with diazoalkane to form the *sym*-azine **4**. Recently, we have investigated in detail the transformations of polyhalogenalkanes $CHal_2XY$ and found that such compounds are partially reduced under COR conditions (inside cycle) [6–9]. The corresponding reduced compound $CBrF_2H$ was detected in the reaction media by ^{19}F NMR spectroscopy (δ: 69.69 ppm; J_{HF}; 62.7 Hz) [10].

It should be noted that two types of alkenes could be obtained according to the mechanism proposed (Scheme 3). $CuBr_2$ or CuBrF could be eliminated from an intermediate organocopper compound **II** formed by addition of complex **I** to CBr_2F_2. However, the olefination with CBr_2F_2 proceeds with excellent chemoselectivity. Only difluoroalkene **3** is formed as a result of elimination of bromine atoms from CF_2Br_2. The other possible product, the corresponding bromofluoroalkene, was not detected in the reaction mixture according to NMR and GC–MS. These results are in good agreement with the considerable difference in bond energy for C–F and C–Br bonds which should be broken in COR (Scheme 3).



Scheme 3.

Table 1
Synthesis of 2,2-difluorostyrenes

Alkene	Entry	Isolated yield (%)		
		Alkene	Azine **4**	Total
	**3a**	36	61	97
	**3b**	26	72	98
	**3c**	20	74	94
	**3d**	20	[a]	[a]
	**3e**	31	[a]	[a]
	**3f**	33	[a]	[a]
	**3g**	29	[a]	[a]

[a] The yield of corresponding azines was not determined.

3. Conclusion

A new simple and convenient method for *one-pot* preparation (2,2-difluorovinyl)benzenes from aromatic aldehydes based on catalytic olefination reaction has been developed. A series of substituted benzaldehydes bearing electron-donating and electron-withdrawing groups could be converted to (2,2-difluorovinyl)benzenes, the yields of the corresponding alkenes were in the range of 20–36%. The advantages of the proposed method are the inexpensive starting materials, the mild reaction conditions and simple handling of the products.

4. Experimental

NMR spectra were recorded on a Varian VXR-400 spectrometer in $CDCl_3$ with TMS as internal standard. Column and TLC chromatography was performed on silica gel Merck 60 and Merck $60F_{254}$ plates respectively. Azines **4a–c** were characterized by comparison of their physical and spectral data with reported recently.

4.1. General procedure for preparation of (2,2-difluorovinyl)benzenes

A solution of aromatic aldehyde (5 mmol) in EtOH (20 ml) was added dropwise to a stirred solution of hydrazine hydrate (5 mmol, 0.25 ml) in EtOH (5 ml) and the mixture was stirred until aldehyde disappeared (3 h, TLC monitoring). Then freshly purified CuCl (50 mg, 0.5 mmol) and 1,2-ethylenediamine (1.7 ml, 25 mmol) were added. After 10 min CBr_2F_2 (0.85 ml, 10 mmol) was added dropwise, maintaining the temperature at 20 °C (water bath). The reaction mixture was stirred for 24 h and quenched with hydrochloric acid (5%) (150 ml). Reaction products were extracted with CH_2Cl_2 (50 ml × 3). Extracts were dried over sodium sulfate, CH_2Cl_2 was evaporated and the residue was purified by column chromatography (hexane or hexane–CH_2Cl_2).

*4.1.1. 1-Chloro-4-(2,2-difluorovinyl)benzene (**3a**)*

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.24 (1H, dd, J_{HF} = 25.9, 3.7 Hz), 7.24 (2H, d, J_{HF} = 8.5 Hz), 7.30 (2H, d, J_{HF} = 8.5 Hz) [11].

*4.1.2. 1-(2,2-Difluorovinyl)-4-methylbenzene (**3b**)*

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.35 (3H, s, Me), 5.25 (1H, dd, J_{HF} = 26.4, 3.8 Hz), 7.16 (2H, d, J_{HF} = 8.2 Hz), 7.24 (2H, d, J_{HF} = 8.2 Hz) [4].

*4.1.3. 1-(2,2-Difluorovinyl)-4-methoxybenzene (**3c**)*

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.78 (3H, s, MeO), 5.19 (1H, dd, J_{HF} = 26.4, 3.8 Hz), 6.85 (2H, d, J_{HF} = 8.8 Hz), 7.23 (2H, d, J_{HF} = 8.8 Hz) [12].

*4.1.4. 1-(2,2-Difluorovinyl)-3-nitrobenzene (**3d**)*

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.37 (1H, dd, J_{HF} = 25.4, 3.1 Hz), 7.50 (1H, dd, J_{HF} = 8.2, 7.9 Hz), 7.63 (1H, d, J_{HF} = 7.9 Hz), 8.08 (1H, d, J_{HF} = 8.2 Hz), 8.17 (1H, c) [4].

*4.1.5. 1-Bromo-4-(2,2-difluorovinyl)benzene (**3e**)*

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.22 (1H, dd, J_{HF} = 25.9, 3.7 Hz), 7.19 (2H, d, J_{HF} = 8.8 Hz), 7.45 (2H, d, J_{HF} = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 81.49 (dd, J_{CF} = 30.3, 12.9 Hz, –CH=), 120.80 (s, C-1), 129.07 (dd, J_{CF} = 6.1, 3.1 Hz, C-3), 129.27 (dd, J_{CF} = 7.6, 6.1 Hz, C-4), 131.79 (s, C-2), 156.32 (dd, J_{CF} = 298.3, 289.1 Hz, CF_2). ^{19}F NMR (376.29 MHz, $CDCl_3$/CCl_3F) δ: −83.58 (d, J_{FF} = 29.7 Hz), −81.76 (dd, J_{FF} = 29.7, 25.9 Hz). Anal. Calcd. for $C_8H_5BrF_2$: C, 43.87; H, 2.30. Found: C, 43.56; H, 2.27.

*4.1.6. 1-(2,2-Difluorovinyl)-4-iodobenzene (**3f**)*

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.20 (1H, dd, J_{HF} = 25.8, 3.5 Hz), 7.04 (2H, d, J_{HF} = 8.5 Hz), 7.63 (2H, d, J_{HF} = 8.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 81.81 (dd, J_{CF} = 30.3, 13.0 Hz, –CH=), 92.45 (s, C-4), 129.36 (dd, J_{CF} = 6.1, 3.1 Hz, C-2), 129.86 (dd, J_{CF} = 7.6, 6.1 Hz, C-1), 137.92 (s, C-3), 156.54 (dd, J_{CF} = 299.0, 289.9 Hz, CF_2). ^{19}F NMR (376.29 MHz, $CDCl_3$/CCl_3F) δ: −83.34 (d, J_{FF} = 29.7 Hz), −81.54 (dd, J_{FF} = 29.7 Hz, J_{HF} = 25.8 Hz). Anal. Calcd. for $C_8H_5IF_2$: C, 36.12; H, 1.89. Found: C, 36.32; H, 1.82.

*4.1.7. 1-tert-Butyl-4-(2,2-difluorovinyl)benzene (**3g**)*

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.31 (9H, s, Me) 5.19 (1H, dd, $J_{HF} = 26.4$, 3.8 Hz), 7.19 (2H, d, $J_{HF} = 8.5$ Hz), 7.29 (2H, d, $J_{HF} = 8.5$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.53 (s, Me), 34.70 (s, **C**$(Me)_3$), 82.05 (dd, $J_{CF} = 29.0$, 13.7 Hz, –CH=), 125.64 (s, C-1), 127.42 (dd, $J_{CF} = 6.1$, 3.1 Hz, C-4), 127.52 (dd, $J_{CF} = 7.6$, 6.1 Hz, C-3), 149.87 (s, C-2), 156.35 (dd, $J_{CF} = 297.5$, 286.8 Hz, CF_2). ^{19}F NMR (376.29 MHz, $CDCl_3/CCl_3F$) δ: −85.80 (d, $J_{FF} = 33.0$ Hz), −82.87 (dd, $J_{FF} = 33.0$ Hz, $J_{HF} = 26.4$ Hz). Anal. Calcd. for $C_{12}H_{14}F_2$: C, 73.45; H, 7.19. Found: C, 73.09; H, 7.34.

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