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Reformatsky Reactions with Propargyl Bromide and Zn – Cu Couple

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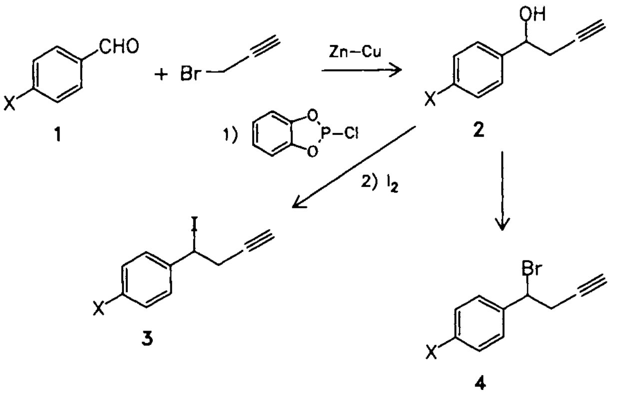
A Reformatsky-type reaction with propargyl bromide and Zn – Cu couple provides easy access to acetylenic carbinols, which can be converted into their iodo and bromo derivatives.

The reactivity of Zn – Cu couple in organic reactions has been described[1]. It has also been shown that in the presence of Zn propargyl bromide undergoes a Reformatsky-type reaction with a variety of carbonyl compounds to give acetylenic carbinols[2]. We describe here the Reformatsky-type reaction of a variety of *para*-substituted benzaldehydes (including alkoxycarbonyl, as shown in Scheme 1), with the organometallic reagent generated from Zn – Cu couple and propargyl bromide. The reaction occurs at the aldehyde, leaving the *para* substituent intact. When this reaction was attempted with Zn in place of Zn – Cu couple it was unsuccessful.

Scheme 1



a: X = H[3)], b: X = CO_2Me, c: X = CN,
d: X = CO_2H, e: X = CO_2tBu

The main advantage of the method is that extremely pure reactants and very careful manipulations are not demanded, in contrast to the classical procedure, where zinc is easily deactivated due to its tendency to be oxidized by air. However, very dry solvents, very pure reactants, and the use of THF instead of benzene increased the yield of carbinols in our modified procedure. The carbinols **2** were obtained in yields of 69 – 83%.

Using known methods[3,4], we further prepared the iodo and bromo derivatives **3** and **4** from the carbinols **2**, in yields of 30 – 65%. These halo derivatives can be used in the synthesis of tetrahydrofolic acid analogs[5].

Experimental

Melting points were determined with a Thomas-Hoover open-capillary melting point apparatus and are uncorrected. – ^{1}H-NMR spectra were determined with a Nicolet QE 300 (300 MHz) spectrometer. – Mass spectra were determined with a AEI MS-9 instrument. – Elemental analyses were carried out by Eli Lilly & Co., Indianapolis, Indiana. Commercial reagents were used without further purification.

General Procedure for the Preparation of the Carbinols **2**: Zn – Cu couple was prepared according to the literature[1c]. A solution of aldehyde **1** (0.02 mol) and propargyl bromide (80% solution in toluene; 3.72 g, 0.025 mol)[6] in dry THF or benzene (10 ml) was added dropwise to Zn – Cu couple in the same solvent (5 ml) with vigorous stirring, such that the mixture remained at gentle reflux. The mixture was heated at reflux for 1 additional h, cooled, acidified[7], extracted with ether, dried, and concentrated. The carbinols **2** were purified by distillation in vacuo or by column chromatography [silica gel, CH_2Cl_2/Et_2O (90:10)] in 69 – 83% yield. Purification of **2** by CC was preferred in the case of the *para*-substituted carbinols, since distillation led to their conversion into elimination products. In all these cases, the carbinol was the second band after some unreacted starting benzaldehyde.

1-Phenyl-3-butyn-1-ol (**2a**): 2.43 g (83%), b.p. 73°C/0.4 Torr (ref.[2] 72°C/0.4 Torr).

Methyl 4-(1-Hydroxy-3-butynyl)benzoate (**2b**): 2.86 g (70%) when benzene was the reaction solvent, 3.26 g (80%) when THF was the reaction solvent; pale yellow oil, not very stable at room temp. – ^{1}H NMR ($CDCl_3$): δ = 2.04 (t, J = 3 Hz, 1H, ≡CH), 2.58 – 2.61 (m, 2H, CH_2), 3.85 (s, 3H, OCH_3), 4.86 (t, J = 6 Hz, 1H, CH), 7.40 (d, J = 9 Hz, 2H, aromatic H), 7.94 (d, J = 9 Hz, 2H, aromatic H).

$C_{12}H_{12}O_3$ Calcd. 204.0786 Found 204.0790 (MS)

4-(1-Hydroxy-3-butynyl)benzonitrile (**2c**): 1.98 g (58%) in benzene, 2.80 g (82%) in THF; a white solid, recrystallization from methylene chloride/ether; m.p. 106 – 108°C. – ^{1}H NMR ($CDCl_3$): δ = 2.10 (t, J = 3 Hz, 1H, ≡CH), 2.62 – 2.66 (m, 2H, CH_2), 4.93 (t, J = 6 Hz, 1H, CH), 7.52 (d, J = 9 Hz, 2H, aromatic H), 7.65 (d, J = 9 Hz, 2H, aromatic H).

$C_{11}H_9NO$ (171.2)	Calcd.	C 77.17	H 5.29	N 8.18
	Found	C 77.11	H 5.39	N 8.07
	Calcd.	171.0684	Found	171.0684 (MS)

4-(1-Hydroxy-3-butynyl)benzoic Acid (**2d**): 3.42 g (71%) in THF; pale yellow oil, which partly crystallized, m.p. 124 – 125°C. – ^{1}H

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NMR ($CDCl_3$): δ = 2.41 (t, J = 3 Hz, 1H, ≡CH), 2.67 – 2.69 (m, 2H, CH_2), 4.98 (t, J = 6 Hz, 1H, CH), 7.52 (d, J = 9 Hz, 2H, aromatic H), 8.10 (d, J = 9 Hz, aromatic H), 10.97 (br., 1H, COOH).

$C_{11}H_{10}O_3$ Calcd. 190.0631 Found 190.0631 (MS)

tert-Butyl 4-(1-Hydroxy-3-butynyl)benzoate (**2e**): 3.39 g (69%) in THF; colorless oil. – ^1H NMR ($CDCl_3$): δ = 1.55 (s, 9H, CMe_3), 2.03 (t, J = 3 Hz, 1H, ≡CH), 2.60 (m, 2H, CH_2), 4.87 (t, J = 6 Hz, 1H, CH), 7.39 (d, J = 9 Hz, 2H, aromatic H), 7.92 (d, J = 9 Hz, 2H, aromatic H).

$C_{15}H_{18}O_3$ Calcd. 246.1256 Found 246.1252 (MS)

General Method for the Preparation of the Bromides **4**: The bromides **4** were prepared from the corresponding carbinols **2** (0.01 mol) with pyridine and phosphorus tribromide, according to the method of Akhtar[3], and purified by CC [silica gel, CH_2Cl_2/Et_2O (9:1), first band], except in the case of **4a**, which was purified by distillation[8,9].

4-Bromo-4-phenyl-1-butyne (**4a**): 1.25 g (60%); pale yellow liquid, b.p. 85 – 87°C/0.4 Torr (ref.[3] b.p. 88 – 89°C/0.5 Torr).

Methyl 4-(1-Bromo-3-butynyl)benzoate (**4b**): 0.91 g (34%); yellow oil, which turned to yellow-orange by the time. – ^1H NMR ($CDCl_3$): δ = 2.06 (t, J = 3 Hz, 1H, ≡CH), 3.07 – 3.11 (m, 2H, CH_2), 3.88 (s, 3H, OMe), 5.04 (t, J = 9 Hz, 1H, CH), 7.47 (d, J = 6 Hz, 2H, aromatic H), 7.99 (d, J = 6 Hz, 2H, aromatic H).

$C_{12}H_{11}BrO_2$ (267.1) Calcd. C 53.95 H 4.15 Br 29.92
Found C 53.88 H 4.11 Br 29.97
Calcd. 265.994 Found 265.9924 (MS)

4-(1-Bromo-3-butynyl)benzonitrile (**4c**): 0.94 g (40%); yellow oil. – ^1H NMR ($CDCl_3$): δ = 2.08 (t, J = 3 Hz, 1H, ≡CH), 3.09 – 3.14 (m, 2H, CH_2), 5.04 (t, J = 9 Hz, 1H, CH), 7.55 (d, J = 6 Hz, 2H, aromatic H), 7.66 (d, J = 6 Hz, 2H, aromatic H).

$C_{11}H_8BrN$ Calcd. 232.9840 Found 232.9837 (MS)

tert-Butyl 4-(1-Bromo-3-butynyl)benzoate (**4e**): 1.08 g (35%); pale yellow oil. – ^1H NMR ($CDCl_3$): δ = 1.58 (s, 9H, CMe_3), 2.06 (t, J = 3 Hz, 1H, ≡CH), 3.12 (m, 2H, CH_2), 5.06 (t, J = 9 Hz, 1H, CH), 7.47 (d, J = 6 Hz, 2H, aromatic H), 7.97 (d, J = 6 Hz, 2H, aromatic H).

$C_{15}H_{17}BrO_2$ Calcd. 308.0412 Found 308.0419 (MS)

General Procedure for the Preparation of the Iodides **3**: The iodides **3** were prepared from the corresponding carbinols **2** (0.005 mol), *o*-phenylene phosphorochloridite, pyridine, and iodine according to the method of Corey[4]. They were purified by CC [silica gel, CH_2Cl_2/Et_2O (90:10), first band].

1-Phenyl-3-butynyl Iodide (**3a**): 0.83 g (65%); yellow-orange oil. – ^1H NMR ($CDCl_3$): δ = 2.16 (t, J = 3 Hz, 1H, ≡CH), 3.21 (m, 2H, CH_2), 5.23 (t, J = 9 Hz, 1H, CH), 7.32 – 7.46 (m, 5H).

$C_{10}H_9I$ Calcd. 255.9712 Found 255.9710 (MS)

Methyl 4-(1-Iodo-3-butynyl)benzoate (**3b**): 0.47 g (30%); orange oil. – ^1H NMR ($CDCl_3$): δ = 2.11 (t, J = 3 Hz, 1H, ≡CH), 3.14 – 3.17 (m, 2H, CH_2), 5.20 (t, J = 9 Hz, 1H, CH), 7.45 (d, J = 6 Hz, 2H, aromatic H), 7.97 (d, J = 6 Hz, 2H, aromatic H).

$C_{12}H_{11}IO_2$ (314.1) Calcd. C 45.88 H 3.53 I 40.40
Found C 45.84 H 3.49 I 40.46

4-(1-Iodo-3-butynyl)benzonitrile (**3c**): 0.91 g (65%); yellow-orange oil. – ^1H NMR ($CDCl_3$): δ = 2.13 (t, J = 3 Hz, 1H, ≡CH), 3.13 – 3.18 (m, 2H, CH_2), 5.18 (t, J = 9 Hz, 1H, CH), 7.53 (d, J = 9 Hz, 2H, aromatic H), 7.62 (d, J = 9 Hz, 2H, aromatic H).

$C_{11}H_8IN$ Calcd. 280.9661 Found 280.9660 (MS)

tert-Butyl 4-(1-Iodo-3-butynyl)benzoate (**3e**): 0.57 g (32%); yellow-orange oil. – ^1H NMR ($CDCl_3$): δ = 1.57 (s, 9H, CMe_3), 2.11 (t, J = 3 Hz, 1H, ≡CH), 3.17 (m, 2H, CH_2), 5.20 (t, J = 6 Hz, 1H, CH), 7.44 (d, J = 9 Hz, 2H, aromatic H), 7.94 (d, J = 9 Hz, 2H, aromatic H).

$C_{15}H_{17}IO_2$ Calcd. 356.0237 Found 356.0235 (MS)

CAS Registry Numbers

1a: 100-52-7 / **1b**: 1571-08-0 / **1c**: 105-07-7 / **1d**: 619-66-9 / **1e**: 65874-27-3 / **2a**: 1743-36-8 / **2b**: 121598-68-3 / **2c**: 121598-69-4 / **2d**: 121598-70-7 / **2e**: 121598-71-8 / **3a**: 121598-75-2 / **3b**: 121598-76-3 / **3c**: 121598-77-4 / **3e**: 121598-78-5 / **4a**: 80605-26-1 / **4b**: 121598-72-9 / **4c**: 121598-73-0 / **4e**: 121598-74-1 / propargyl bromide: 106-96-7

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[6] In the case of **2d**, 7.44 g (0.05 mol) of propargyl bromide was used instead of 3.72 g (0.025 mol) due to the carboxyl group of **1d**.

[7] In the case of **2e**, acidification of the reaction mixture should be done very carefully, so that hydrolysis of the *tert*-butyl ester is avoided.

[8] Elimination during distillation of *para*-substituted **4** and **3** was even more pronounced than in the case of the carbinols **2**.

[9] **4d**, **3d** have not been prepared.

[139/89]