

PREPARATION OF HIGHLY FUNCTIONALIZED 3,4-DISUBSTITUTED **CYCLOBUTENE-1,2-DIONES** USING FUNCTIONALIZED ZINC-COPPER **ORGANOMETALLICS**

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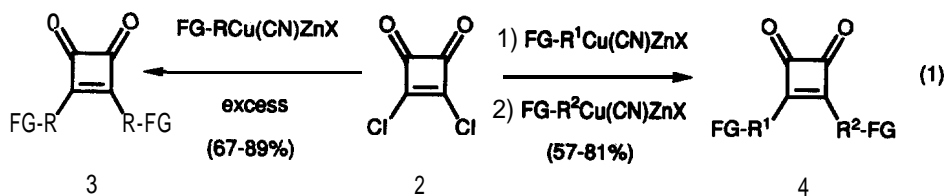
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Summary: The selective substitution reactions of the zinc-copper reagents with 3,4-dichlorocyclobutene-1,2-dione **2** allows to prepare a variety of new functionalized symmetrical and mixed 2,4-disubstituted cyclobutene-1,2-diones of type **3** and **4**.

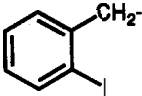
Synthetic methods for the preparation of 3,4-disubstituted cyclobutene-1,2-diones¹ have been developed by a number of research groups due to the importance of these compounds as building blocks for organic synthesis² and for the preparation of new materials³.

We wish now to report a new approach to highly functionalized 3,4-disubstituted cyclobutene-1,2-diones by using the addition of functionalized zinc-copper reagents **FG-RCu(CN)ZnX** **1** to the readily available 3,4-dichlorocyclobutene-1,2-dione⁵ **2**. Depending on the nature of the reagents **1** and on the stoichiometry used, either symmetrical cyclobutenediones **3** or unsymmetrical cyclobutenediones **4** are obtained in fair to good yields (eq. 1).



Thus, the addition of **3,4-dichlorocyclobutene-1,2-dione 2** (1.0 equiv.) to a THF solution of a functionalized copper-zinc reagent FG-RCu(CN)ZnI (ca. 3 equiv.) at -78°C (then 0°C , 2 h) affords the desired symmetrical di-coupling products **3a-i** in 87-89% isolated yield⁶, see eq. 1 and Table 1.

Table 1. Symmetrically functionalized **3,4-disubstituted cyclobutene-1,2-diones 3a-i** obtained by the reaction of **3,4-dichlorocyclobutene-1,2-dione 2** with FGRCu(CN)ZnX 1.

Entry	RCu(CN)ZnX	R	Product of type 3	Yield (%) ^a
1	1a	$\text{Bu-C}\equiv\text{C}-(\text{CH}_2)_3-$	3a	81
2	1b	$\text{H-C}\equiv\text{C}-(\text{CH}_2)_3-$	3b	79
3	1c	PhCH_2-	3c	67
4	1d	$\text{Ph}-\underset{\text{he}}{\text{CH}}-$	3d	78
5	1e		3e	79
8	1f	$\text{AcO}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$	3f	89
7	1g	$\text{EtOOC}-\text{CH}_2-\text{CH}_2-\text{CH}_2-$	3g	83
8	1h	$\text{NC}-\text{CH}_2-\text{CH}_2-\text{CH}_2-$	3h	83
9	1i	$\text{Ph}-\text{C}(=\text{O})-\text{CH}_2-\text{CH}_2-\text{CH}_2-$	3i	72

^a All yields refer to isolated yield of analytically pure compounds

Remarkably, a wide range of functionalities (alkyne (entries 1 and 2), ester (entries 6 and 7), halide (entry 5), nitrile (entry 8) and ketone (entry 9) are tolerated in the organometallic reagents 1, allowing a *unique access* to functionalized **cyclobutene-1,2-diones** of type 3. A selective replacement of one chlorine atom of 2 is possible and the addition of the copper reagents derived respectively from cyclohexenylzinc iodide and 3-carbethoxypropylzinc iodide provides the expected **4-mono-substituted-3-chlorocyclobutene-1,2-diones 5** in moderate yields (respectively 42 and 52%). An important side product (up to 40% in the case of **1g**) is the corresponding symmetrical **adduct** of type 3. A better procedure consists of adding sequentially to the dichloride 2 (1.0 equiv.) two different copper reagents $\text{FG-R}^1\text{Cu(CN)ZnX}$ (ca. 1.2 equiv, -60° to -40°C , 4h) and $\text{FG-R}^2\text{Cu(CN)ZnX}$ (ca. 1.8 equiv. -78° to 0°C , 1 h). In this one-pot procedure the sensitive mono-substituted **3-chlorocyclobutene-1,2-diones 5** are generated in situ and are reacted directly with an excess of the second zinc-copper reagents $\text{FG-R}^2\text{Cu(CN)ZnX}$. If FG-R^1 is a secondary or tertiary group, then good overall yields of the mixed disubstituted cyclobutenediones 4 are obtained; (**57-81%**, see eq. 1 and Table 2).

Table 2. Mixed disubstituted **cyclobutene-1,2-diones** **4** obtained by the sequential reaction of **3,4-dichlorocyclobutene-1,2-dione** **2** with two different copper zinc reagents **FG-R¹Cu(CN)ZnX** and **FG-R²Cu(CN)ZnX**.

Entry	FG-R ¹	FG-R ²	Product of type 4	Yield (%) ^a
1	c-Hex	(CH ₂) ₃ CO ₂ Et	4a	74
2	c-Hex	(CH ₂) ₅ OAc	4b	67
3	c-Hex	(CH ₂) ₃ CN	4c	65
4	c-Hex	(CH ₂) ₄ Cl	4d	57
5	t-Bu	(CH ₂) ₃ CO ₂ Et	4e	81
6	t-Bu	(CH ₂) ₃ CN	4f	77

^a All yields refer to isolated yields of analytically pure products.

In summary, we have shown that symmetrical and mixed polyfunctional **3,4-disubstituted cyclobutene-1,2-diones** of type 3 and 4 can be readily prepared. The use of these and related cyclobutenes for the preparation of new polymers is currently investigated.

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References and Notes

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6. Typical procedure: Preparation of **3,4-bis-(5-acetoxypentyl)cyclobutene-1,2-dione 3f** (entry 6 of Table 1). A THF solution of **5-iodopentyl acetate** (3.1 g, 12 mmol in 6 mL of THF) was added **dropwise** at 35°C to zinc dust (2.4 g, 36 mmol) which had been activated with **1,2-dibromoethane** and **Me₃SiCl** according to ref. 4a. The reaction mixture was stirred for 2 h at **35-40°C** and the excess of zinc dust was decanted. The clear solution of **5-acetoxypentylzinc iodide** was added at **-20°C** to a THF solution of **CuCN·2LiCl** (made from **CuCN** (1.06 g, 12 mmol), **LiCl** (1.0 g, 24 mmol) and THF (10 mL)). After stirring for 5 min at 0°C, the reaction mixture was cooled to -70°C and **3,4-dichlorocyclobutene-1,2-dione** (604 mg, 4 mmol) in THF (3 mL) was added. After 2 h at this temperature, the resulting red solution was warmed to 0°C, stirred for 2 h at this temperature and worked up as usual. The resulting crude oil was purified by flash-chromatography using **EtOAc/hexane (15:85)** affording analytically pure **3f** (1.21 g, 89% yield).
7. Typical Procedure: Preparation of **4-(3-carbethoxypropyl)-3-cyclohexylcyclobutene-1,2-dione 4a** (entry 1 of Table 2). Cyclohexylzinc iodide prepared from cyclohexyl iodide (1.47 g, 7 mmol), zinc dust (1.3 g, 20 mmol) in THF (7 mL) at **35-40°C** (2 h) was added at -10°C to a THF (7 mL) solution of **CuCN** (540 mg, 6 mmol) and **LiCl** (500 mg, 12 mmol). The resulting solution was stirred 5 min at 0°C and cooled to -70°C and a solution of **3,4-dichlorocyclobutene-1,2-dione** (755 mg, 5 mmol) in THF (7 mL) was slowly added. The reaction mixture was stirred 4 h at -40°C to -60°C cooled to -70°C and the copper reagent derived from **3-carbethoxypropylzinc iodide** (prepared from ethyl 4-iodobutyrate (2.42 g, 10 mmol) zinc (2.0 g, 30 mmol), **CuCN** (900 mg, 10 mmol), **LiCl** (840 mg, 20 mmol) in 7 and 10 mL of THF; see above) was added. The reaction mixture was slowly warmed to 0°C and stirred for 1 h at this temperature. After the usual workup, the crude residual oil was purified by flash chromatography affording first 0.3 g (24%) of **3,4-dicyclohexylcyclobutene-1,2-dione** (hexane), followed by 1.034 g (74% yield) of the desired mixed adduct **48** (hexane/EtOAc = 95:5).

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