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Tandem coupling reactions of benzynes and 1,3-diones: a novel synthesis of 2,2-diphenyl-1,3-diones

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Abstract—A novel, general, and mild method is described to prepare 2,2-diphenyl-1,3-diones with benzyne using CuBr and trichloroacetic acid as the catalyst.

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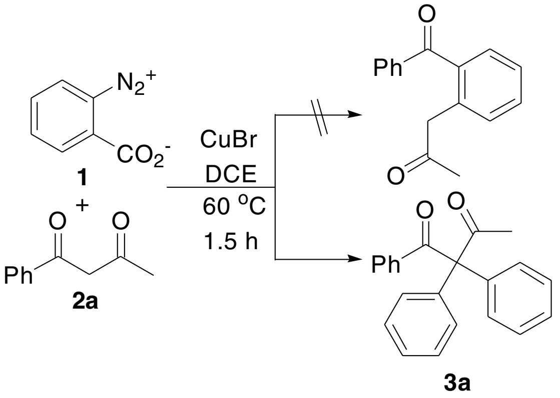
Arynes are highly reactive intermediates, which have been widely used in organic synthesis.[1,2] The recent reports on formation,[3] reactivity,[4] and particular application[5] of arynes illustrate the continued interest in this area. Nucleophilic addition is a direct approach to the syntheses of substituted benzenes. The addition of alcohols, amines, sulfonamides, carbamates, phenols, and carboxylic acids to arynes can be considered formally as the insertion of the arynes into heteroatom-hydrogen bonds.[6] Recently, the insertion of arene into the α,β single bond of β-ketoesters,[2a] α-cyanocarbonyl compounds, and 1,3-diones was also reported.[7] These reactions led to the acyl-alkylation of arynes to produce interesting *ortho*-disubstituted arenes. Herein, we report a novel tandem reaction of benzyne with 1,3-diones to furnish 2,2-diphenyl-1,3-diones under mild conditions.

Benzenediazonium-2-carboxylate (**1**) is a benzyne precursor, which is easily prepared from anthranilic acid.[3d,e] It can in situ generate benzyne at moderate temperature.[8] Initially, we used **1** as the benzyne precursor to react with one equivalent of 1-phenylpentane-1,3-dione (**2a**) in the presence of catalyst CuBr. We surprisingly found that the reaction did not produce the benzyne insertion product, but afforded α,α-diphenyl-substituted 1,3-dione **3a** in 15% yield (Scheme 1). We then optimized the conditions for this reaction (Table 1). The best yield of **3a** was obtained using CuBr (5 mol %)[9] and trichloroacetic acid (5 mol %) as the co-catalyst system and DCE as the solvent (Table 1, entry 18).



Scheme 1.

Encouraged by this result, our next goal was to broaden the substrate scope to a variety of 1,3-diones using the optimized conditions. It was found that a wide range of substrates gave moderate to good yields (Table 2, entries 1–21).[10] The *ortho*-substituted 1-phenyl-1,3-diones gave moderate yields due to steric hindrance (Table 2, entries 4–7), while 1-phenyl-1,3-diones bearing a strong electron-donating group gave relatively low yield (Table 2, entries 17–20). All products were analyzed by IR, ^{1}HNMR, ^{13}CNMR, and MS spectra as well as elemental analysis.[11]

Buchwald and co-workers reported a copper-catalyzed arylation of diethyl malonate.[9c] However, the method is only suitable for the synthesis of α-monoarylmalonates. Additionally, Barton et al.[12] reported a synthesis of 2,2-diphenyl-1,3-dicarbonyl compounds via the

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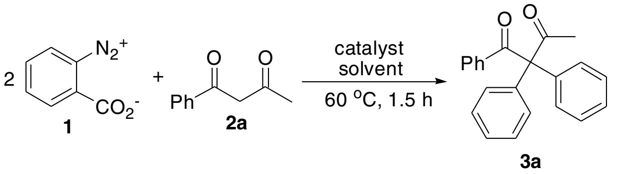
Table 1. Optimization of reaction conditions for coupling of benzyne with 1,3-dione **2a**[a]



Entry	Catalyst (mmol)	Solvent	Yield[b] (%)
1	—	DCE	—
2	CuCl/0.02	DCE	Trace
3	CuCl/0.04	DCE	Trace
4	CuBr/0.02	DCE	10
5	CuBr/0.04	DCE	15
6	CuBr/0.1	DCE	18
7	CuI/0.04	DCE	Trace
8	$CuCl_2$/0.1	DCE	—
9	$CuBr_2$/0.1	DCE	—
10	CuI_2/0.1	DCE	—
11	CCl_3CO_2H/0.04	DCE	24
12	CCl_3CO_2H/0.1	DCE	26
13	CuBr/0.1 + CH_3COOH/0.1	DCE	30
14	CuBr/0.04 + CCl_3CO_2H/0.04	DCE	75
15	CuBr/0.1 + CCl_3CO_2H/0.04	DCE	80
16	CuBr/0.2 + CCl_3CO_2H/0.04	DCE	81
17	CuBr/0.04 + CCl_3CO_2H/0.1	DCE	83
18	CuBr/0.1 + CCl_3CO_2H/0.1	DCE	90
19	CuBr/0.2 + CCl_3CO_2H/0.2	DCE	90
20	CuBr/0.1 + CCl_3CO_2H/0.1	DCE	75[c]
21	CuBr/0.1 + CCl_3CO_2H/0.1	DCE	64[d]
22	CuBr/0.1 + CCl_3CO_2H/0.1	THF	50
23	CuBr/0.1 + CCl_3CO_2H/0.1	MeCN	45

[a] Reaction conditions: **1** (4 mmol), **2a** (2 mmol), solvent (30 mL), 60 °C, 1.5 h.

[b] Isolated yield by silica gel column chromatography.

[c] **1** (6 mmol).

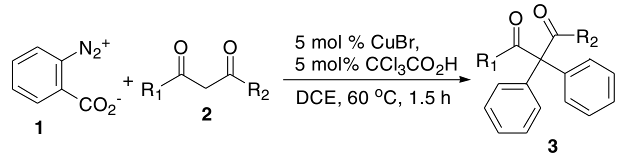
[d] **1** (7 mmol).

phenylation of enolate anions of 1,3-dicarbonyl compounds using pentavalent organobismuth reagents. Compared with this method, our procedure is general, mild, and efficient. Furthermore, the present method does not require a large amount of metalic reagents and atmosphere sensitive reagents.

A plausible mechanism is illustrated for the construction of this class of quarternary stereocenters in Scheme 2. The tandem process involves two nucleophilic additions of enol of 1,3-dione to the in situ generated benzyne. Copper salt and organic acid Cl_3CCO_2H could promote the formation of enol and hence catalyze the cascade reaction. CuX may play a crucial role in the formation, a six-member ring transition state. For this purpose, CuBr is a better catalyst than $CuBr_2$.

In summary, we have developed a novel and general method for the 2,2-bisphenylation of 1,3-diones with benzyne using CuBr and trichloroacetic acid as the catalysts. This method provides an efficient route to a wide variety 2,2-diphenyl-1,3-diones from readily available starting materials under mild conditions. Further studies on the synthetic applications of this procedure are underway.

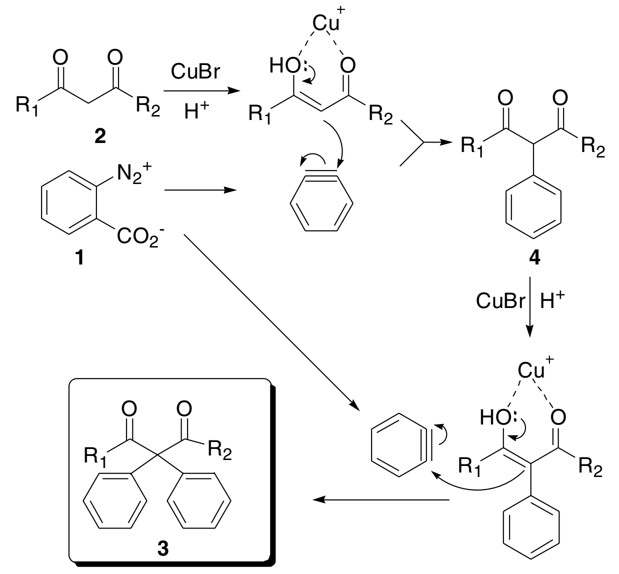
Table 2. 2,2-Diphenyl-1,3-diones **3** from benzene-diazonium-2-carboxylate (**1**) and 1,3-diones **3**[a]



Entry	Product	R_1	R_2	Yield[b] (%)
1	**3a**	Ph	Me	90
2	**3b**	Ph	Et	81
3	**3c**	Ph	Ph	82
4	**3d**	$2\text{-}FC_6H_4$	Me	75
5	**3e**	$2\text{-}FC_6H_4$	Et	73
6	**3f**	$2\text{-}ClC_6H_4$	Me	74
7	**3g**	$2\text{-}ClC_6H_4$	Et	72
8	**3h**	$3,5\text{-}Br_2C_6H_3$	Me	90
9	**3i**	$3,5\text{-}Br_2C_6H_3$	Et	82
10	**3j**	$4\text{-}ClC_6H_4$	Et	84
11	**3k**	$4\text{-}ClC_6H_4$	C_3H_7	65
12	**3l**	$4\text{-}BrC_6H_4$	Et	83
13	**3m**	$4\text{-}CF_3C_6H_4$	Et	85
14	**3n**	$4\text{-}EtC_6H_4$	Me	75
15	**3o**	$4\text{-}EtC_6H_4$	Et	70
16	**3p**	$4\text{-}MeC_6H_4$	Et	72
17	**3q**	$3\text{-}MeOC_6H_4$	Me	70
18	**3r**	$3\text{-}MeOC_6H_4$	Et	66
19	**3s**	$3\text{-}MeOC_6H_4$	C_3H_7	60
20	**3t**	$4\text{-}MeOC_6H_4$	Me	68
21	**3u**	Me	Me	88

[a] Reaction conditions: **1** (4 mmol), **2** (2 mmol), CuBr (0.1 mmol) and trichloroacetic acid (0.1 mmol), DCE (30 mL), 60 °C, 1.5 h.

[b] Isolated yield.



Scheme 2.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.09.092.

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10. *General procedure for the synthesis of 2,2-diphenylpentane-1,3-diones* **3**. To a solution of 1,3-dione **2** (2 mmol), trichloroacetic acid (0.10 mmol) and CuBr (0.10 mmol) in DCE (5 mL) was added a suspension of benzenediazonium-2-carbolylate (4 mmol) in DCE (30 mL) at 60 °C over a period of 1.5 h, the color changed from light yellow to deep brown. After completion of the reaction as indicated by TLC, the solvent was evaporated in vacuum and the residual oil was purified by silica gel column chromatography using hexane–EtOAc (20:1, v/v) as the eluant to afford **3**. The product was recrystallized from hexane–EtOAc.
11. *Spectra data of representative compounds*. Compound **3a**: Colorless solid; mp 124–125 °C; IR (KBr): 1718, 1655, 1595, 1444, 1231 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, $J = 7.0$ Hz, 2H), 7.40–7.32 (m, 11H), 7.24 (t, $J = 7.9$ Hz, 2H), 2.10 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.4, 198.0, 136.9, 136.2, 133.0, 130.83, 130.81, 128.7, 128.3, 128.1, 79.3, 29.7 ppm; MS (ESI): m/z 337 ($[M + Na]^+$); Anal. Calcd for $C_{22}H_{18}O_2$: C, 84.05; H, 5.77. Found: C, 84.04; H, 5.77. Compound **3b**: Colorless solid; mp 97–98 °C; IR (KBr): 1725, 1663, 1594, 1447, 1232 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, $J = 8.6$ Hz, 2H), 7.37–7.28 (m, 11H), 7.25–7.20 (m, 2H), 2.30 (q, $J = 7.3$ Hz, 2H), 0.96 (t, $J = 7.3$ Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.0, 198.3, 137.0, 136.3, 132.9, 130.9, 130.8, 128.6, 128.3, 128.0, 79.3, 35.6, 10.0 ppm; MS (ESI): m/z 351 ($[M+Na]^+$); Anal. Calcd for $C_{23}H_{20}O_2$: C, 84.12; H, 6.14. Found: C, 84.14; H, 6.12. Compound **3s**: Colorless solid; mp 90–91 °C; IR (KBr): 1717, 1664, 1580, 1485, 1264 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.29 (m, 12H), 7.10 (t, $J = 8.0$ Hz, 1H), 6.92 (t, $J = 6.2$ Hz, 1H), 3.65 (s, 3H), 2.29 (t, $J = 7.5$ Hz, 2H), 1.50–1.45 (m, 2H), 0.72 (t, $J = 7.4$ Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.8, 198.1, 159.4, 137.6, 136.9, 131.0, 129.2, 128.6, 128.0, 123.6, 119.8, 114.8, 79.4, 55.5, 44.1, 19.0, 13.9 ppm; MS (ESI): m/z 395 ($[M+Na]^+$); Anal. Calcd for $C_{25}H_{24}O_3$: C, 80.62; H, 6.49. Found: C, 80.61; H, 6.49.
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