Copper(I) Iodide Catalyzed Formation of Aryl Hydrazides from a Mitsunobo Reagent and Aryl Halides

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Abstract: The Mitsonubo reagent (triphenylphosphine and dialkyl azodicarboxylates) was employed as a potential anionic nucleophile in a reaction involving aryl halides to produce aryl hydrazides. Aryl iodides and bromides, with electron-withdrawing as well as electron-releasing groups on the aromatic ring, undergo coupling reactions in good yields. The optimized conditions are developed for aryl iodides at room temperature and for aryl bromides at 60–75 °C.

Key words: aryl iodide, aryl bromide, Mitsonubo reagent, aryl hydrazide, copper(I) iodide

Aryl hydrazides are important subunits in a wide range of pharmaceuticals and bioactive agents.^{1,2} Dialkyl azodicarboxylates (DAAD) have been used in the preparation of hydrazides,³ which are useful precursors in the synthesis of amines.⁴ New methods such as amination of aryl Grignard reagents,⁵ aryllithium reagents,⁶ and aryl zinc halides⁷ with DAAD have been developed for the synthesis of hydrazides. However, these reactions are limited to electron-rich arenes because they proceed via an electrophilic substitution.⁸ Recently, Buchwald reported the synthesis of *N*-aryl hydrazides by amination of aryl iodides with hydrazides.⁹ In addition, Chatani has reported the synthesis of *N*-aryl hydrazides from the reaction of arylboronic acids and DAAD in the presence of copper salts.¹⁰

In this Letter, we report a mild procedure for the synthesis of aryl hydrazides from the reaction of the Mitsunobu reagent system [triphenylphosphine (Ph₃P) and DAAD] with aryl halides in good yields (Scheme 1).¹¹ Investigations started with the coupling reaction of Ph₃P with diisopropyl azodicarboxylate (1b) and iodobenzene (2a) in the presence of copper(I) iodide as catalyst. When the reaction of equimolar amounts of Ph₃P with 1b and 2a was performed in the presence of CuI (0.025 mmol) in toluene at room temperature for 20 hours under nitrogen, phenyl hydazide 3b was obtained in 10% yield together with diisopropyl hydrazodicarboxylate in 65% yield (Table 1). After screening a variety of solvents and catalysts, the best results were obtained in THF at room temperature for 16 hours in the presence of 10 mol% of CuI. Decreasing the amount of CuI to 5 mol%, resulted in incomplete consumption of iodobenzene (Table 1). Under these optimized conditions, the diisopropyl hydrazodicarboxylate was not detected in the reaction mixture.

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Table 1Optimization Reaction Conditions for the Formation ofAryl Hydrazides from Aryl Iodides, Ph3P, and DAAD

Catalyst	Solvent	Yield (%) Catalyst ^a	Solvent	Yield (%) ^b	
CuI	DMSO	65	Cu	THF	n.r.	
CuI	DMF	55	CuCl	THF	72	
CuI	toluene	15	CuBr	THF	20	
CuI	THF	92	Cu ₂ O	THF	35	
CuI	MeCN	78	Cu(OAc) ₂	THF	trace	
CuI	dioxane	46	CuCl ₂ CuI ^c	THF THF	trace 80	

^a 10 mol% catalyst unless stated otherwise.

^b Reaction time16 h.

^c 5 mol% catalyst, reaction time was 24 h.

Subsequently, a variety of substituted aryl iodides was tested under the optimized reaction conditions, and the results are summarized in Scheme 1. Aryl iodides having electron-rich, electron-deficient, or bulky groups on the aromatic ring afforded good to excellent yields.

Ph ₃ P ⁺ RO ₂ C	`N≂I	_CO₂R N	+ /	٩rl	Cul THF, r.t.	R	0 ₂ C ^{-N} N ^{-C} H	℃ ₂ R
	1a 1b	R Et <i>i</i> -Pr	2a 2b 2c 2d 2e 2f	Ar Ph 4-Tol 4-O ₂ I 4-Me 2-CF 4-BrC	NC6H4 OC6H4 3C6H4 2C6H4	3a 3b 3c 3d 3e 3f 3g 3h 3i	$\begin{array}{l} \text{Ar} \\ \text{Ph} \\ \text{Ph} \\ \text{4-Tol} \\ \text{4-Tol} \\ \text{4-O_2NC_6H_4} \\ \text{4-O_2NC_6H_4} \\ \text{4-MeOC_6H_4} \\ \text{2-CF_3C_6H_4} \\ \text{4-BrC_6H_4} \end{array}$	R Et <i>i</i> -Pr Et <i>i</i> -Pr <i>i</i> -Pr <i>i</i> -Pr <i>i</i> -Pr

Scheme 1

When aryl bromides were subjected to the reaction conditions developed for the aryl iodides (Table 1), no aryl hydrazides were detected in the reaction mixture. After screening a variety of solvents and catalysts, the best results were obtained in MeCN at 60–75 °C for 16 hours in the presence of 10 mol% of CuI and 20 mol% of Phen (1,10-phenanthroline) as a ligand¹² (Table 2). Subsequently, a variety of substituted aryl bromides was tested under the optimized reaction conditions, and the results are summarized in Scheme 2.¹³

 Table 2
 Optimization Reaction Conditions for Aryl Bromides

Catalyst	Solvent	Yield (Yield (%)Catalyst ^a		Yield (%) ^t	
CuI	DMSO	73	Cu	MeCN	n.r	
CuI	DMF	61	CuCl	MeCN	78	
CuI	toluene	15	CuBr	MeCN	32	
CuI	THF	70	Cu ₂ O	MeCN	28	
CuI	MeCN	90	Cu(OAc) ₂	MeCN	trace	
CuI	dioxane	78	CuCl ₂ CuI ^c	MeCN MeCN	trace 80	

^a 10 mol% catalyst unless stated otherwise; Phen 20 mol%.

^b Reaction time 20 h.

^c 5 mol% catalyst, reaction time was 26 h.

Ph ₃ P + RO ₂ C	N≈ _N ∕CO₂R	+ ArBr	Cul, Phen MeCN, reflux	Ar I RO ₂ C ^N N H	.CO ₂ R
1a 1b	R Et 2g <i>i</i> ·Pr 2h 2i 2j 2k 2l	Ar 3-Tol 1-naphth 4-NCC ₆ H 2-O ₂ NC ₆ 3-F ₃ CC ₆ 2-thienyl	nyl 3 H ₄ 3 H ₄ 3 H ₄ 3 H ₄ 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3	Ar j 3-Tol k 3-Tol il 1-naphthyl im 1-naphthyl im 4-NCC ₆ H ₄ io 2-O ₂ NC ₆ H ₄ iq 3-F ₃ CC ₆ H ₄ iq 3-F ₃ CC ₆ H ₄ is 2-thienyl	R Et <i>i</i> -Pr Et <i>i</i> -Pr Et <i>i</i> -Pr Et <i>i</i> -Pr

Scheme 2

The optimized reaction conditions given above were compatible with the presence of functional groups, such as CN, NO_2 , CF_3 , OMe, and halogen, on the aromatic ring of the aryl halide. Various aryl bromides afforded the corresponding aryl hydrazides in good to excellent yields.

In summary, the Mitsonubo reagent system has been employed as a potential anionic nucleophile in a reaction involving aryl halides to produce aryl hydrazides. Aryl bromides and iodides with electron-withdrawing as well as electron-releasing groups undergo these coupling reactions in good yields. In this methodology, the optimized conditions have been developed for aryl iodides at room temperature and for aryl bromides at 60–75 °C. The advantages of this methodology are the use of the air-stable, inexpensive CuI catalyst under mild reaction conditions.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(11) Typical Procedure for the Preparation of Aryl Hydrazides 3a–i

To a stirred solution of aryl iodide (1 mmol) and Ph₃P (0.263 g, 1 mmol) in THF (2 mL), was added CuI (9 mg, 0.05 mmol) in one portion. The mixture was stirred at r.t. for 30 min under N₂. Then, the DAAD (1.2 mmol) was added to the reaction mixture, which was stirred at r.t. for 18 h under nitrogen. After removal of the solvent, the residue was purified by chromatography (silica gel, hexane–EtOAc = 5:1) to give hydrazides **3a–i**.

Representative Analytical Data

Diethyl 1-Phenyl-hydrazine-1,2-dicarboxylate (3a) Colorless solid, mp 81–83 °C; yield 0.23 g (91%). IR (KBr): $v_{max} = 3280$, 1599, 1518, 1340, 1100 cm⁻¹. ¹H NMR (500.1 MHz, CDCl₃): $\delta = 1.27$ (3 H, t, ³*J* = 7.0 Hz, Me), 1.28 (3 H, t, ³*J* = 7.0 Hz, Me), 4.22 (4 H, m, 2 CH₂O), 7.09 and 7.19 (1 H, br s, NH), 7.20 (1 H, t, ³*J* = 7.1 Hz), 7.33 (2 H, t, ³*J* = 7.6 Hz), 7.42 (2 H, d, ³*J* = 7.4 Hz). ¹³C NMR (125.7 MHz, CDCl₃): $\delta = 14.4$ (Me), 14.5 (Me), 62.3 (CH₂O), 63.0 (CH₂O), 124.3 (2 CH, br), 126.3 (2 CH), 128.6 (CH), 141.7 (C), 155.0 (C=O), 156.4 (C=O). MS: *m/z* (%) = 252 (1) [M⁺], 180 (10), 152 (100), 134 (16), 108 (22), 107 (69), 106 (14), 91 (17), 77 (32). Anal. Calcd (%) for C₁₂H₁₆N₂O₄ (252.27): C, 57.13; H, 6.39; N, 11.10. Found: C, 57.59; H, 6.44; N, 11.23.

Diisopropyl 1-Phenyl-hydrazine-1,2-dicarboxylate (3b) Colorless solid, mp 90–92 °C; yield 0.25 g (92%). IR (KBr); $v_{max} = 3241, 1569, 1500, 1325, 1110 \text{ cm}^{-1}. ^{1}\text{H} \text{ NMR} (500.1 \text{ MHz, CDCl}_3): \delta = 1.26 (6 \text{ H, t, }^{3}J = 6.6 \text{ Hz, 2 Me}), 1.29 (6 \text{ H, t, }^{3}J = 6.8 \text{ Hz, 2 Me}), 5.08–5.10 (2 \text{ H, m, CHO}), 6.96 and 7.12 (1 \text{ H, br s, NH}), 7.20 (1 \text{ H, t, }^{3}J = 7.1 \text{ Hz}), 7.36 (2 \text{ H, t, }^{3}J = 7.1 \text{ Hz}), 7.36 (2 \text{ H, t, }^{3}J = 7.1 \text{ Hz}), 7.46 (2 \text{ H, d, }^{3}J = 7.4 \text{ Hz}). ^{13}\text{C} \text{ NMR} (125.7 \text{ MHz, CDCl}_3): \delta = 21.0 (2 \text{ Me}), 21.7 (2 \text{ Me}), 70.0 (CHO), 70.7 (CHO), 121.2 (2 CH, br), 125.9 (2 CH), 128.9 (CH), 139.3 (C), 154.7 (C=O), 156.0 (C=O). \text{MS: } m/z (\%) = 280 (1) [M^+], 194 (16), 152 (100), 134 (11), 108 (19), 107 (65), 106 (12), 91 (14), 77 (25). Anal. Calcd (\%) for C_{14}H_{20}N_2O_4 (280.32): C, 59.99; H, 7.19; N, 9.99. Found: C, 59.69; H, 7.24; N, 9.93..$

(12) Typical Procedure for the Preparation of Aryl Hydrazides 3j–s

To a stirred solution of aryl bromide (1 mmol), Ph_3P (0.263 g, 1 mmol), and Phen (0.036 g, 20 mol%) in MeCN (2 mL)

was added CuI (9 mg, 0.05 mmol) in one portion. The mixture was stirred at r.t. for 30 min under N_2 . Then, the DAAD (1 mmol) was added to the reaction mixture, which was stirred at 60–75 °C for 16 h under N_2 . After removal of the solvent, the residue was purified by chromatography (silica gel, hexane–EtOAc = 5:1) to give hydrazides **3j–s**. **Representative Analytical Data**

Diethyl 1-(3-Methylphenyl)-hydrazine-1,2-dicarboxylate (3j)

Yellow oil; yield 0.22 g (83%). IR (KBr): $v_{max} = 3310, 1539, 1510, 1321, 1132 \text{ cm}^{-1}$. ¹H NMR (500.1 MHz, CDCl₃): $\delta = 1.27$ (3 H, t, ${}^{3}J = 7.2$ Hz, Me), 1.30 (3 H, t, ${}^{3}J = 7.1$ Hz, Me), 2.32 (3 H, s, Me), 4.20 (4 H, m, 2 CH₂O), 6.96 and 7.07 (1 H, br s, NH), 7.12 (1 H, d, ${}^{3}J = 7.2$ Hz, CH), 7.20 (1 H, d, ${}^{3}J = 7.3$ Hz, CH), 7.26 (1 H, s, CH), 7.45 (1 H, t, ${}^{3}J = 7.2$ Hz, CH). 13 C NMR (125.7 MHz, CDCl₃): $\delta = 19.6$ (Me), 19.9 (Me), 26.6 (Me), 67.6 (CH₂O), 68.2 (CH₂O), 125.4 (CH, br), 130.3 (CH, br), 133.6 (CH), 136.3 (CH), 141.2 (C), 143.8 (C), 156.5 (C=O), 161.5 (C=O). MS: m/z (%) = 266 (1) [M⁺], 194 (13), 166 (100), 148 (16), 122 (14), 120 (68), 105

(17), 91 (8). Anal. Calcd (%) for C₁₃H₁₈N₂O₄ (266.29): C, 58.63; H, 6.81; N, 10.52. Found: C, 58.83; H, 6.88; N, 10.69. **Diisopropyl 1-(3-Methylphenyl)-hydrazine-1,2dicarboxylate (3k)**

Yellow oil; yield 0.24 g (81%). IR (KBr): $v_{max} = 3291, 1527, 1524, 1314, 1112 cm^{-1}. {}^{1}H NMR (500.1 MHz, CDCl_3):$ $<math>\delta = 1.17$ (6 H, d, ${}^{3}J = 7.2$ Hz, Me), 1.28 (6 H, t, ${}^{3}J = 7.1$ Hz, Me), 2.32 (3 H, s, Me), 4.97–4.99 (2 H, m, 2 CHO), 6.67 and 6.71 (1 H, br s, NH), 6.90 (1 H, d, ${}^{3}J = 7.2$ Hz, CH), 6.97 (1 H, d, ${}^{3}J = 7.3$ Hz, CH), 7.20 (1 H, s, CH), 7.28 (1 H, t, ${}^{3}J = 7.2$ Hz, CH). ${}^{13}C$ NMR (125.7 MHz, CDCl_3): $\delta = 21.6$ (2 Me), 21.9 (2 Me), 29.6 (Me), 70.6 (CHO), 70.8 (CHO), 121.4 (CH, br), 124.3 (CH, br), 126.6 (CH), 128.3 (CH), 138.2 (C), 141.8 (C), 154.5 (C=O), 156.5 (C=O). MS: *m/z* (%) = 294 (1) [M⁺], 208 (13), 166 (100), 148 (16), 122 (14), 120 (68), 105 (17). Anal. Calcd (%) for C₁₅H₂₂N₂O₄ (294.35): C, 61.21; H, 7.53; N, 9.52. Found: C, 61.42; H, 7.62; N, 9.60.

(13) The reaction of aryl bromides was improved in the presence of Phen.

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