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Mild Room-Temperature Palladium-Catalyzed C3-Arylation of 2(1*H*)-Pyrazinones via a Desulfitative Kumada-Type Cross-Coupling Reaction†

Vaibhav P. Mehta, Sachin G. Modha, and Erik Van der Eycken*

Laboratory for Organic & Microwave-Assisted Chemistry (LOMAC), Department of Chemistry, University of Leuven, Celestijnenlaan 200F, B-3001 Leuven, Belgium

erik.vandereycken@chem.kuleuven.be

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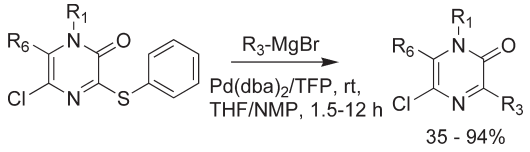

An efficient desulfitative Kumada-type cross-coupling protocol is reported for the C3-arylation of 5-chloro-3-(phenylsulfanyl)pyrazin-2(1*H*)-ones. The method has also been successfully extended to the arylation of some (hetero)aryl thioethers and thioesters.

The use of a transition-metal catalyst for C−C[1] and C−heteroatom[2] cross-coupling reactions has revolutionized the art and practice of organic synthesis in the last couple of decades.[1] The generally mild reaction conditions, high functional group tolerance, and broad availability of the reagents have contributed to the success of these bond-forming reactions. Although in most of these protocols a Pd(0) catalyst[3a,b] is used, other transition metals such as Cu(I),[3c] Ni(0),[3d] Co(II),[3e] and Fe(II or III)[3f−i] have also been investigated. These procedures involve the coupling of an activated or unactivated electrophilic partner[4] with a nucleophilic organometallic donor. The use of organo−sulfur compounds as the electrophilic reaction partner has also been described.[5] Inspired by recent developments in the field of desulfitative[6a−c] C−C cross-coupling methodologies using organometallic donors like organoborons,[6d] organostannanes,[6e] and organozinc[6f] and as a result of our recent investigations on the desulfitative Hiyama-type cross-coupling,[6g] we were keen to explore the use of Grignard reagents (GR) as organometallic partners[7] for the desulfitative C−C bond formation. GR are economical and easy to synthesize,[7d] and many of them are commercially available. The coupling of an aryl GR with an aryl halide is one of the most powerful and versatile approaches for the construction of a variety of biaryls, terphenyls, and oligoaryls, which are important building blocks for the synthesis of natural products and bioactive compounds.[8] A number of nickel and palladium complexes have been reported to catalyze the coupling of GR with aryl bromides and iodides.[9] In a recent report by Vogel and co-worker[10] the use of iron catalysts for the desulfitative C−C cross-coupling reaction applying sulfonyl chlorides and GR was described. Other substrates, including vinyl sulfides, have also been reported to undergo cross-coupling. Early reports by Wenkert[11] and Takei[12] independently revealed that alkenyl and allyl sulfides could undergo Ni-catalyzed Kumada type cross-coupling.[13]

† Dedicated to Academician Prof. Dr. Oleg. N. Chupakin on the occasion of his 75th birthday.

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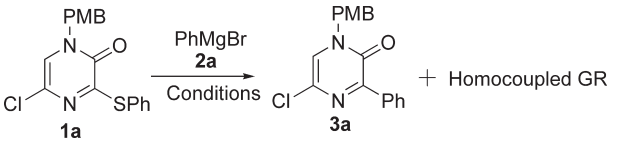
TABLE 1. Preliminary Screening of the Conditions for the Desulfitative Cross-Coupling Reaction[a]

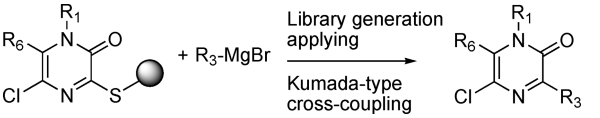


entry	conditions catalyst (mol %), ligand (mol %), solvent (in case 3:1), *T*, time, GR	ratio[b] **3a/1a/**[c]
1	$Fe(acac)_3$ (5), THF, 65 °C, 8 h, 2.0 equiv	0/99/c
2	$Fe(acac)_3$ (5), THF/NMP, 80 °C, 6 h, 2.0 equiv	0/99/c
3	$Ni(OAc)_2$ (5), PPh_3 (10), THF, 65 °C, 6 h, 2.0 equiv	0/99/c
4	$Pd(dba)_2$ (5), TFP (10), THF, 65 °C, 3 h, 2.0 equiv	15/80/c
5[d]	**$Pd(dba)_2$ (5), TFP (10), THF/NMP, rt, 3 h, 1.2 equiv**	**96**[e]**/1/c**
6	$Pd(PPh_3)_4$ (5), THF/NMP, rt, 5 h, 1.2 equiv	75/20/c
7	THF/NMP, rt, 16 h, 1.2 equiv	0/99/c
8	$Pd(PPh_3)_2Cl_2$ (5), THF/NMP, rt, 6 h, 1.2 equiv	50/39/c
9	Herrmann's palladacycle (5), THF/NMP, rt, 4 h, 1.2 equiv	72/24/c
10	$Pd(dba)_2$ (5), THF/NMP, rt, 6 h, 1.2 equiv	60/40/c
11	$Pd(dba)_2$ (5), SPhos (10), THF/NMP, rt, 5 h, 1.2 equiv	20/75/c
12	$Pd(dba)_2$ (5), BINAP (10), THF/NMP, rt, 8 h, 1.2 equiv	2/95/c
13	$Pd(dba)_2$ (5), TBP·HBF_4 (10), THF/NMP, rt, 4 h, 1.2 equiv	92/5/c
14	$Pd(dba)_2$ (5), TMEDA (10), THF/NMP, rt, 8 h, 1.2 equiv	5/94/c
15	$Pd(dba)_2$ (2), TFP (10), THF/NMP, rt, 6 h, 1.2 equiv	50/45/c
16[f]	$Pd(dba)_2$ (5), TFP (10), THF/NMP, rt, 3 h, 1.2 equiv	0/100/c
17[g]	$Pd(dba)_2$ (5), TFP (10), THF/NMP, rt, 3 h, 2.0 equiv	10/90/c
18[h]	$Pd(dba)_2$ (5), TFP (10), THF/NMP, rt, 3 h, 2.0 equiv	0/96/c

[a]Compound **1a** (0.3 mmol) was mixed with catalyst (mol %) and ligand (mol %). The flask was flushed three times with argon, and the mixture was dissolved in the indicated solvent. The flask was flushed three more times with argon, and then phenylmagnesium bromide **2a** (1.0 M in THF, 1.2−2.0 equiv) was added via syringe and the reaction was allowed to stir for the stipulated time. [b]Ratio based on GC−MS analysis. [c]Homocoupled GR was detected. [d]Dropwise addition of GR using syringe drive at a flow rate of 2 mL/h. [e]92% isolated yield (single run). [f]Reaction mixture was cooled to −78 °C, and then GR was added dropwise. [g]Reaction mixture was dissolved at rt and then cooled to 0 °C; GR was added dropwise, and the mixture was allowed to stir at rt. [h]PhMgCl (2 equiv, 2.0 M in THF) was used. TFP = tri-2-furylphosphine, SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl, (±)BINAP = (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene, TBP·HBF_4 = tri-*tert*-butylphosphonium tetrafluoroborate, TMEDA = tetramethylethylenediamine, NMP = *N*-methyl-2-pyrrolidinone, acac = acetylacetonate.

However, (hetero)aryl thioethers have scarcely been reported in the literature.[12b,14] Due to our long withstanding interest in the chemistry of 2(1*H*)-pyrazinones,[15] we have been exploring several methods for the efficient transition-metal-catalyzed C3-decoration of the scaffold.[16a] In view of generating small libraries of C3-arylated compounds,[16b−e] we previously developed a solid-phase organic synthesis (SPOS) approach applying a thiophenyl linker which could simultaneously be cleaved and substituted (traceless linking) resulting in C3-arylation of the pyrazinones scaffold by applying a Liebeskind−Srogl cross-coupling protocol.[16f] We were now eager to know whether a desulfitative Kumada-type coupling could equally do this job, as this should broaden the scope of potential substituents at the C3-position of the pyrazinone scaffold (Scheme 1). As a proof of concept we examined this reaction in the solution phase, mimicking the sulfur linker with a thiophenol substituent.

SCHEME 1. Traceless Linking Concept using a Desulfitative Kumada-Type Cross-Coupling



First we evaluated the application of $Fe(acac)_3$[10] or $Ni(OAc)_2/PPh_3$[17] as catalyst for the desulfitative cross-coupling (Table 1, entries 1−3). Unfortunately, after several hours of heating, the corresponding cross-coupled product could not be observed, and only an extensive amount of aryl−aryl homocoupling product along with starting material was formed. Therefore, we switched to the use of Pd[18] as catalyst. We first studied the application of $Pd(dba)_2$ with TFP (tri-2-furylphosphine) as ligand and THF as solvent at a temperature of 65 °C for 3 h (Table 1, entry 4). A mixture of the desired cross-coupled product along with starting material (15:80) was obtained as was determined by GC−MS

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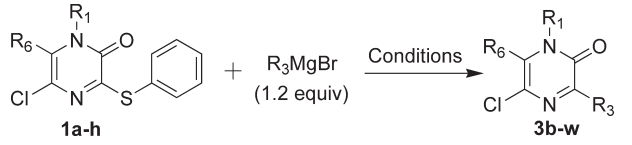
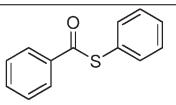
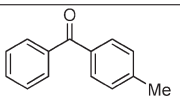
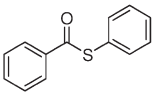
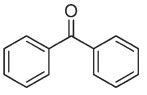
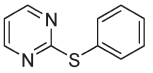
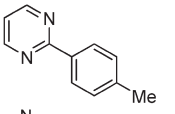
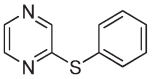
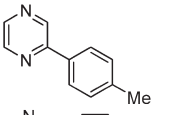
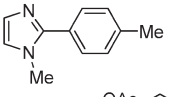
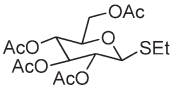
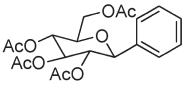
TABLE 2. Evaluation and Scope of the Optimized Cross-Coupling Protocol[a]



entry	R^1	R^6	R^3	product	time (h)	yield[b] (%)
1	PMB	H	Ph	**3a**	3	92
2	PMB	H	4-Me-Ph	**3b**	3	82
3	PMB	H	4-MeO-Ph	**3c**	2.5	94
4	PMB	H	2-thienyl	**3d**	3	92
5	PMB	H	1-naphthyl	**3e**	4	84
6	PMB	H	2-MeO-Ph	**3f**	6	64
7	PMB	H	Ph-acetylene	**3g**	4.5	89
8	PMB	H	Ethyl	**3h**	1.5	63
9[c]	PMB	H	Vinyl	**3i**	2	82
10	PMB	Me	Ph	**3j**	3	74
11	PMB	Me	4-Me-Ph	**3k**	3	79
12	PMB	Me	4-MeO-Ph	**3l**	2.5	68
13	PMB	Me	2-thienyl	**3m**	5	< 5[d,e]
14	PMB	Me	1-naphthyl	**3n**	6	traces[d,e]
15	PMB	Me	2-MeO-Ph	**3o**	8	traces[d,e]
16	PMB	4-MeO-Ph	Ph	**3p**	4	82
17	PMB	Bn	Ph	**3q**	5	59[d]
18	PMB	H	octyl	**3r**	2.5	68
19[f]	PMB	H	Ph	**3a**	4.5	72
20	Ph	Me	Ph	**3s**	12	35[e]
21	Ph	Me	4-Me-Ph	**3t**	12	traces[d,e]
22	Bn	Me	Ph	**3u**	6	71
23	CH_2-Cy	H	Ph	**3v**	8	70
24	$(CH_2)_3$-Ph	H	Ph	**3w**	6	69

[a]Compounds **1a**−**h** (0.3 mmol) were mixed with $Pd(dba)_2$ (5 mol %) and TFP (10 mol %). The flask was then flushed three times with argon, and the mixture was dissolved in THF/NMP (3:1) (4 mL) and again flushed three times with argon. Then GR (1.2 equiv) was added dropwise using a syringe drive at a flow rate of 2 mL/h, and the reaction was allowed to stir for the stipulated time at rt. [b]Isolated yields are reported (average of two runs). [c]1.5 equiv of GR was used. [d]No C−C cross-coupling product was observed; only starting material was recovered. [e]Homocoupling of GR was observed. [f]*S*-ethyl was used instead of *S*-phenyl.

TABLE 3. Application of the Optimized Cross-Coupling Protocol for Some Thioethers and Thioesters

entry[a]	reactant	product	time (h)	yield (%)[b]
1			1.5	96
2			2	92
3			3	84
4			3	87
5			6	0[c]
6			4	23[d]

[a]Compounds **4a**−**8a** (0.5 mmol) were mixed with $Pd(dba)_2$ (5 mol %) and TFP (10 mol %). The flask was then flushed three times with argon; the mixture was dissolved in THF/NMP (3:1) (4 mL) and again flushed three times with argon. Then GR (1.2 equiv) was added dropwise using a syringe drive at a flow rate of 2 mL/h, and the reaction was allowed to stir for the stipulated time at rt. [b]Isolated yields are reported (single runs). [c]No cross-coupled product was observed, and the starting material was fully decomposed after 6 h. [d]All starting material was consumed after 4 h.

analysis. It is worth mentioning that 2.0 equiv of GR was added in one shot after the reaction mixture was flushed with argon at 65 °C. Therefore, the obtained low conversion could probably be rationalized by the fast homocoupling of GR. We then examined the addition of GR in a dropwise fashion using a syringe drive at a flow rate of 2 mL/h at room temperature (Table 1, entry 5). The solvent system was changed from THF to THF/NMP mixture (3:1) using 5 mol % of $Pd(dba)_2$ and 10 mol % of TFP ligand. To our full satisfaction, the desired product could be isolated in 92% by applying different reaction conditions that were examined after 3 h of stirring at rt. Different Pd catalysts and ligands applying different reaction conditions were examined; however, the best results were obtained with the conditions of entry 5 (Table 1). Finally, we also checked the applicability of phenylmagnesium chloride for this cross-coupling reaction that was carried out at 65 °C for 3 h. However, TLC and MS analysis confirm the presence of starting material in the reaction mixture (Table 1, entry 18).

Encouraged by these findings, we explored the scope of this protocol. An array of phenylsulfinylated pyrazinones **1a**−**h** (Table 2) were reacted with various alkyl- or (hetero)arylmagnesium bromides using our optimized conditions.[19] In most cases, the reactions proceeded well affording the cross-coupled product in good to excellent yields (Table 2, entries 1−12). When pyrazinones bearing a methyl substitution at the 6-position were reacted with heteroaryl or sterically hindered GR, the reaction did not proceed, even after an extended reaction time (Table 2, entries 13−15). Also with a phenyl substitution in 1-position, the reaction either proceeded partially or not at all (Table 2, entry 20, 21).

Having successfully established the methodology for the pyrazinone scaffold, we next explored the scope of the protocol for some thioethers and thioesters. Gratifyingly, the diaryl ketones **4b**,**c** were obtained in high yields starting from the thioester **4a** (Table 3, entries 1 and 2). The reaction also proceeded well with heteroaryl thioethers **5a** and **6a** (Table 3, entries 3 and 4). However, when 1-methylimidazole was used, exclusive decomposition of the starting material was observed (Table 3, entry 5). Interestingly, when ethyl

(19) We preferred to use aryl-, heteroaryl-, and alkylmagnesium bromides instead of magnesium chlorides as the latter are insufficiently reactive.

2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside was reacted with phenylmagnesium bromide, 23% of the desired arylated product **8b** was observed after 4 h along with decomposition of the starting material (Table 3, entry 6).

In summary, an efficient protocol for the C3-functionalization of variously substituted 5-chloro-3-(phenylsulfanyl)-pyrazin-2(1*H*)-ones was successfully elaborated by applying a desulfitative Kumada-type cross-coupling. The method was also extended to some thioesters and (hetero)aryl thioethers. The application of this desulfitative cross-coupling for the C3-decoration of the 2(1*H*)-pyrazinone scaffold via solid-phase organic synthesis is under current investigation.

Experimental Section

Typical Procedure for the Synthesis of Representative Compound 3a. Under air, an oven-dried, two-necked flask equipped with a stir bar was charged with thioether **1a** (0.29 mmol, 100 mg), $Pd(dba)_2$ (5 mol %, 8 mg), and TFP (10 mol %, 7 mg), sealed with a septum, and purged with argon. Distilled THF/NMP (3:1) (4 mL) was added by syringe, and the mixture was stirred for 1−2 min. The reaction mixture initially became dark red and changed to bright yellow. The flask was again flushed three times with argon, and the mixture was allowed to stir for 15 min. Then the Grignard reagent **2a** (0.36 mmol, 76 mg) (1.0 M solution in THF) was added under argon over 15 min applying a syringe drive at a flow rate of 2 mL/min. The reaction mixture was allowed to stir for approximately 3 h at rt, and the reaction was monitored by GC/MS and/or TLC analysis. After completion of the reaction, HCl (1 N) was added, and the mixture was stirred for 15 min and extracted with diethyl ether (2 × 50 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure and the residue was subjected to column chromatography over silica gel applying a mixture of EtOAc/heptane ranging from 5% to 20% to afford compound **3a** in 92% yield.

Compound 3a (5-chloro-3-phenyl-1-(4-methoxybenzyl)-2(1*H*)-pyrazinone): yellow oil in 92% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36−8.33 (m, 2H), 7.44−7.42 (m, 3H), 7.31−7.28 (d, 2H, J = 8.2 Hz), 7.16 (s, 1H), 6.91−6.88 (d, 2H, J = 9.12 Hz), 5.04 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 160.10, 154.50, 152.24, 134.94, 130.74, 130.46, 129.37, 128.21, 126.56, 126.35, 125.22, 114.68, 55.41, 52.48; HRMS (EI) calcd for $C_{18}H_{15}O_2N_2Cl$ 326.0822, found 326.0817.

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Supporting Information Available: Experimental procedure and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.