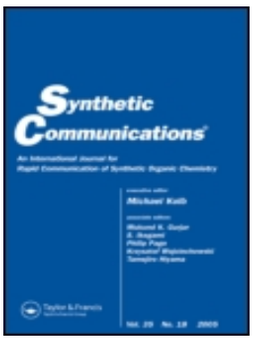

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Aryl C-N bond formation by electrophilic amination of diarylcadmium reagents with *O*-substituted ketoximes

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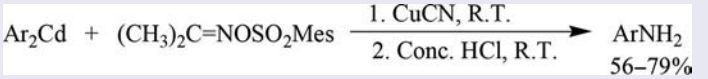
ABSTRACT

Diorganocadmium reagents cannot react with ketoxime at room temperature. CuCN catalysis allows diarylcadmium reagents to react with ketoxime and to give corresponding arylamines in good to high yields at room temperature. According to the electronic effects of the substituent attached to the aromatic ring, functionalized diarylcadmium reagents show *meta-para* selectivity in their amination reactions. Also compared to diarylzinc reagents, diarylcadmium reagents react with *O*-substituted ketoxime under milder reaction conditions and they form corresponding arylamines in higher yields. CuCN cannot help dialkyl-, dicycloalky-, and dibenzylcadmium reagents to react with ketoxime. Our Aryl C-N bond formation method does not include cadmium excretion into the environment.

GRAPHICAL ABSTRACT



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Introduction

Electrophilic amination of organometallic reagents is an important and useful synthetic method for the synthesis of organic compounds bearing amino functionality and is continuing to gain the attentions of chemists.[1,2] To date, various procedures for C-N bond formation by electrophilic amination of organomagnesium,[3–6] organozinc,[7–12] and organocopper reagents[12–17] have been reported. Organocadmium reagents have been mostly used for the synthesis of ketones from acid halides or acid anhydrides. They have been also used for regioselective alkylation of quinones.[18,19] Recently diarylcadmium reagents prepared by depronative cadmation using $LiCd(TMP)_3$ (prepared from LiTMP and $CdCl_2 \cdot$ TMEDA (*N,N,N′,N′*-tetramethylethylenediamine)) have been reacted with some electrophiles successfully.[20–22] To our knowledge, there has not been any publication about electrophilic amination of organocadmium reagents with oximes to date.

Previously, our research group described high-yielding processes for electrophilic amination of organozinc reagents.[23–25] Organozinc reagents are prepared using $ZnCl_2$ or $ZnBr_2$ and both of these zinc compounds are hygroscopic. Therefore, extra care and precautions are needed while working with these compounds. Organocadmiums can tolerate

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several functional groups and therefore allow synthesis of functionalized organic compounds, like organozinc reagents. For this reason, we had concluded that examining C-N bond formation using organocadmium reagents would be useful in terms of synthetic organic chemistry.

Results and discussion

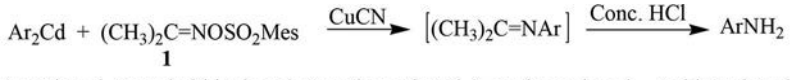
In this article, reaction of diaryilcadmium reagents with ketoxime under catalyst-free conditions, a CuCN-catalyzed aryl C-N bond-formation method, and the determination of applicability of this method using functionalized diarylcadmiums are given.

We used acetone *O*-(2,4,6-trimethylphenylsulfonyl)oxime **1**, which is a sp^2-*N* containing reagent and reacts with organometallic reagents by displacement of the mesitylsulfonyloxy group to give an imine, as aminating agent (Scheme 1). Diarylcadmium reagents were prepared by transmetallation of the corresponding arylmagnesium bromides with CdI_2 in tetrahydrofuran (THF) and controlled by Gilman's color test.[26] Amination reaction was performed by cannulation of THF solution of **1** into organocadmium reagent. Since CdI_2 is not a hygroscopic compound, it was too easy to work with it compared to zinc halides.

Arylamines as the final products were removed from the reaction mixture as their benzamide derivatives and these known compounds were identified from their melting points[27,28] and ^{1}H NMR analysis.[28–32] Cadmium was removed from reaction mixture as a white-colored salt ($Cd(OH)_2$) during basification of the reaction mixture after hydrolysis with concentrated HCl. Thereby cadmium was not discarded as waste.

Reaction of diphenylcadmium with **1** under catalyst-free reaction conditions at room temperature to furnish aniline resulted in failure (Table 1, entry 1). For this reason, we decided to try CuCN catalysis: 10 mol% CuCN helped diphenylcadmium to react with ketoxime, but the yield of aniline was low (entry 2). Decreasing the amount of CuCN from 10 mol% to 5 mol% led to a dramatic yield increase (entry 3). When reaction time was kept less than 90 min the yield started to decrease (entries 3–5). The highest yield was obtained when reaction was run for 90 min at room temperature in the presence of 5 mol% CuCN (entry 6). Less than 1 mmol of diphenylcadmium was not sufficient to obtain aniline in high yield (entry 8). Use of $CdCl_2$ for the preparation of diphenylcadmium led to slight decrease in yield; in addition $CdCl_2$ is too hygroscopic and it was difficult to work with it (entry 9). Use of phenyllithium, prepared in ether, instead of PhMgBr in THF for the preparation of diphenylcadmium led to decrease in the yield of aniline (entry 10).

After setting the optimal reaction conditions, we turned our attention to examine the scope of the electrophilic amination method that we developed for diarylcadmiums. Electron-withdrawing or electron-releasing substituted anilines were synthesized in good



Scheme 1. Aryl C-N bond formation by electrophilic amination of diarylcadmiums with acetone *O*-(2,4,6-trimethylphenylsulfonyl)oxime.

Table 1. CuCN-catalyzed electrophilic aminaton of Ph_2Cd.

Entry	CuCN (%)	Time (min)	$PhNH_2$ (%)
1	—	60	—
2	10	60	41
3	5	60	72
4	5	45	61
5	5	30	56
6	5	90	78
7	2.5	90	48
8	5	90	42[b]
9	5	90	68[c]
10	5		50[d]

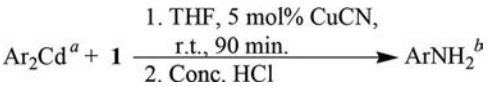
[a]Ph_2Cd/ketoxime = 1:1.
[b]Ph_2Cd/ketoxime = 0.8:1.
[c]Ph_2Cd was prepared using $CdCl_2$ instead of CdI_2.
[d]Ph_2Cd was prepared using PhLi /Et_2O.
[e]Yield of aniline was isolated as its benzamide derivative.

to high yields under optimized reaction conditions (Table 2). In the reaction of $+M > -I$ type group substituted diarylcadmiums with **1**, *meta*-functionalized aniline was obtained in higher yield than *para*-functionalized aniline (entries 3 and 4). In contrast, in the case of $-I >> +M$ type substituent, diarylcadmium bearing the substituent at the *para*-position gave better yield than *meta*-substituted diarylcadmium (entries 5 and 6).

Naphtylamine was afforded in moderate yield. Alkyl-, cycloalkyl-, and benzylcadmium reagents gave unsuccessful reactions with ketoksime.

The data obtained from this study showed that aryl C-N bond formation reaction using diarylcadmium reagents is higher yielding than the same reaction of diarylzinc reagents.[11,12] For example, both aniline and 4-anisylamine were obtained in 51% yields using corresponding diarylzinc reagents in the presence of 20% mol of CuCN at room temperature, in 3 h. As seen in Table 2, these amines obtained in higher yields (78% and 71% respectively) using corresponding diarylcadmium reagents in the presence of 4 times less amount of CuCN without any need to use cosolvent or additive, at room temperature in 1.5 h. In

Table 2. Functionalized arylamine preparation using Ar_2Cd.



Entry	Ar	$ArNH_2$ (%)
1	C_6H_5	78
2	4-$CH_3SC_6H_4$	79
3	4-$CH_3OC_6H_4$	71
4	3-$CH_3OC_6H_4$	77
5	4-ClC_6H_4	75
6	3-ClC_6H_4	68
7	3,5-$(Cl)_2C_6H_3$	71
8	4-FC_6H_4	63
9	2,5-$(CH_3)_2C_6H_3$	64
10	1-Naphtyl	56

[a]Ar_2Cd/ketoxime = 1:1.
[b]Yields of amines were isolated as their benzamide derivatives.

addition, since organocadmium reagents were prepared using nonhygroscopic CdI_2, it was easier to work with them compared to organozinc reagents.

Conclusions

In summary, this work contains the first data about the electrophilic amination of diorganocadmium reagents with ketoximes. We have shown that arylamines can be synthesized at room temperature using diarylcadmium reagents in the presence of 5 mol% CuCN, without any cadmium excretion into the environment.

Experimental

All reactions involving organocadmium reagents were performed in flame-dried glassware with standard syringe / cannula techniques[33] under an atmosphere of dry, oxygen-free argon. Melting points were determined on a Gallencamp capillary melting point. ^{1}H NMR spectra were recorded in $CDCl_3$ or dimethylsulfoxide (DMSO-d_6) at room temperature on a Varian-Mercury 400-MHz (FT) NMR spectrometer. All chemical shifts were given in parts per million (ppm) downfield from tetramethylsilane (TMS).

THF was freshly distilled from solution of sodium / benzophenone under dry argon. Copper(I) cyanide was purified prior to use[34] and kept under a dry argon atmosphere.

Magnesium turnings for Grignard reactions (Fischer) and cadmium iodide (Merck) were used without any purification. Aryl bromides (Sigma-Aldrich) were in high purities and used without any further purification.

Organomagnesium bromides were prepared in THF by conventional standard methods and their concentrations were determined by the method of Watson and Eastham.[35]

Acetone *O*-(2,4,6-trimethylphenylsulfonyl)oxime **1** was prepared and purified according to the method described in the literature.[36]

General procedure: CuCN-catalyzed electrophilic amination of diphenylcadmium with acetone O-(2,4,6-trimethylphenylsulfonyl)oxime

A solution of CdI_2 (0.3664 g, 1 mmol) in anhydrous THF (3 ml) was cooled to −3 °C under an argon atmosphere and 2 mmol of phenylmagnesium bromide in THF was added dropwise by syringe. The reaction mixture was stirred for an additional 10 min, the cooling bath was removed, and the resulting suspension was stirred at room temperature for 10 min. To this mixture, CuCN (0.05 mmol 5%) and a solution of **1** (1 mmol) in dry THF (2 ml) were added. The reaction mixture was stirred at room temperature for 1.5 h and then worked up by addition of concentrated HCl and stirred overnight at room temperature. The aqueous phase was washed with diethyl ether (2 × 50 ml) and made basic with concentrated NaOH, and the free amine was extracted with diethyl ether (3 × 50 ml). The organic layer was dried over Na_2SO_4, the solvent was evaporated, and the crude product was converted to its *N*-benzoyl derivative by reaction with benzoyl chloride in the presence of NaOH. The product was recrystallized from ethanol–water (4:1). Mp: 160–162 °C (lit.[27] 160 °C); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ_H 7.96 (s, 1 H), 7.85–7.88 (m, 2 H), 7.64–7.67 (m, 2 H), 7.52–7.56 (m, 1 H), 7.44–7.48 (m, 2 H), 7.34–7.39 (m, 2 H), 7.13–7.17 (m, 1 H).

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