chemistry proceedings

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Proceeding Paper

On Novel Non-Organometallic Aryl Nucleophile in Palladium-Catalyzed Arylation †

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† Presented at The 28th International Electronic Conference on Synthetic Organic Chemistry (ECSOC 2024), 15–30 November 2024; Available online: https://sciforum.net/event/ecsoc-28.

Abstract: Phenylazocarboxylate is described as novel non-organometallic aryl nucleophile in palladium-catalyzed arylation

Keywords: arylation; non-organometallic nucleophile; arylazocarboxylate

1. Introduction

The arylation of aromatic electrophiles (halogenoaromatics, triflates, diazoniums) catalyzed by palladium is known [1–3] with numerous organometallic aryl nucleophiles of boron (Suzuki-Miyaura), silicon (Hiyama), tin (Stille), zinc (Negishi), mercury (Heck) [4] which obviously leads to sub -products containing metals (Figure 1).

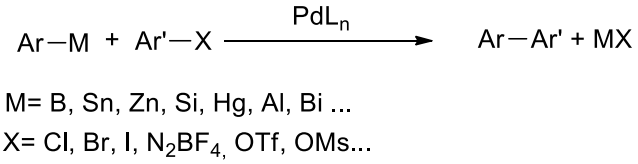


Figure 1. Arylation of aromatic electrophiles with aryl organometallics as nucleophiles.

If boron and silicon are only slightly or not toxic, a large majority of metals present a toxicity which can be annoying during the synthesis of molecules for therapeutic purposes. This is particularly the case for tin in the Stille reaction.

2. Results and Discussion

We investigated the opportunity to use a non-organometallic phenyl anion derived from an elimination reaction as a nucleophilic arylation agent. Several tests using a carboxylate or a sulfinate were not successful, but on the other hand phenylazocarboxylate led to interesting results.

Phenylazacarboxylate was first introduced by Nesmeyanov and Reutov in the synthesis of arylmercury and arylantimony componds [5,6].

To the best our knowledge, this compound was not reused and was never tested in catalyzed palladium couplings. During phenylation, one molecule of nitrogen and one molecule of carbon dioxide are removed (Figure 2).

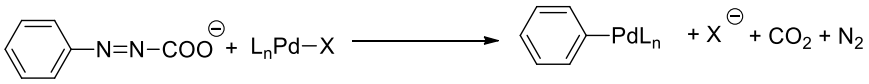


Figure 2. Arylation of palladium by phenylazocarboxylate.

Citation: Villemin, D.; Jullien, A.; Bar, N. On Novel Non-Organometallic Aryl Nucleophile in Palladium-Catalyzed Arylation. *Chem. Proc.* **2024**, *6*, x. https://doi.org/10.3390/xxxxx

Academic Editor(s): Name

Published: 15 November 2024

The precursor of phenylazocarboxylate is the commercially available as 1-phenylsemicarbazide, which can be oxidised to furnish 1-phenyldiazocarboxamide (Figure 3). The latter can be converted into potassium phenylazacarboxylate by saponification with potassium hydroxide, under ultrasound irradiation, without heating, in a yield of 81% (Figure 3).

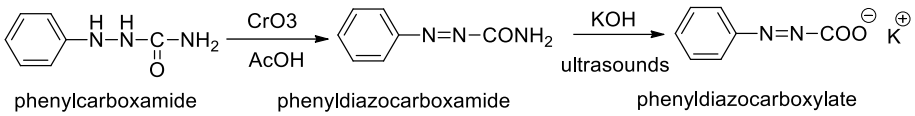


Figure 3. Formation of phenyldiazocarboxamide and phenyldiazocarboxylate.

Several coupling tests of this phenylazacarboxylate were carried out with palladium catalysts with potassium hydroxide as a base with MSTPP as a ligand or with cesium carbonate with a carbene ligand formed with H-Imes, Cl.

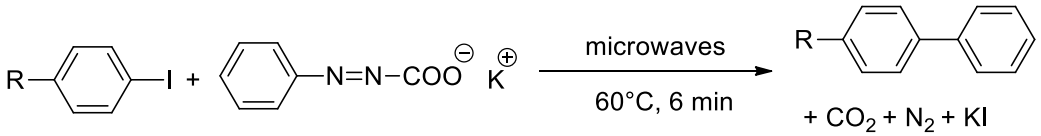


Figure 4. Couplings of phenylazacarboxylate**.**

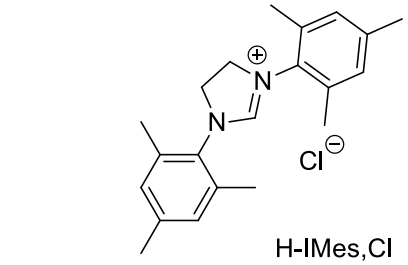
A mixture of products, benzene, diphenyl and coupling product were formed during the reaction. An excess of potassium azocarboxylate (2 equivalents relative to the electrophile) led to better coupling product yields. The reaction with potassium phenylazocarboxylate gave a better yield of coupling product at 60 °C than at 35 °C under microwave irradiation. Results obtained are reported in Table 1. Ligands used in the couplings are reported in Figure 5.

Table 1. Coupling of phenylazacarboxylate in the presence of palladium catalysts.

Entry	R	Conditions	Yield (%) of C_6H_5Ar
1	H	a, MW 60 °C, 6 min	68
2	CH_3	a MW 60 °C, 6 min	62
3	OCH_3	a MW 60 °C, 6 min	58
4	$COOCH_3$	a MW 60 °C, 6 min	75
5	NO_2	a MW 60 °C, 6 min	80
6	H	b MW 60 °C, 6 min	75
7	OCH_3	b MW 60 °C, 6 min	60

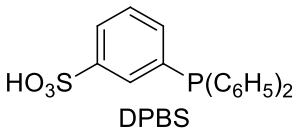
(a) Potassium phenylazacarboxylate/R-C_6H_4-I/$Pd_2(dba)_3$/DPBS/KOH = 2/1/0.01/0.04/2 dioxane/water = 10/1, microwaves 60 °C, 6 min. (b) Potassium phenylazacarboxylate/R-C_6H_4-I/$Pd_2(dba)_3$/HIMes,Cl/Cs_2CO_3 = 2/1/0.01/0.04/1**;** Dioxane/acetonitrile = 1/1,microwaves 60 °C, 6 min.

It therefore appears that arylazocarboxylates can be non-organometallic arylnucleophiles in aromatic arylations.



H-IMes,Cl

1,3-dimesityl-4,5-dihydro-1*H*-imidazol-3-ium chloride



DPBS

3-(diphenylphosphino)benzenesulfonic acid

Figure 5. Ligands used in aryl couplings.

3. Experimental

3.1. General Information

The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brüker DPX 250 and DPX 400 spectrometer at 250 and 400 MHz. Samples were recorded in $CDCl_3$ solutions using TMS as an internal standard. The chemical shifts are expressed in δ units (ppm) and quoted downfield from TMS.

The various analyses were carried out by GC/MS to identify the products, which were then measured by GC (Varian CP 3800(GC) and Saturn 2000 (MS/MS), column CPSIL8CB (30 m × 0.25 nm) 220 °C, gaz He.)

Microwave irradiations were performed at 2450 MHz with a Prolabo Synthewave 402 under argon.

3.2. Starting Products

1-phenyldiazocarboxamide, RN:4203-28-5.

7.55 g of 1-phenylsemicarbazide (0.05 mol) are dissolved in 150 mL of glacial acetic acid. 5 g of chromic anhydride in 50 mL of water are then added slowly while stirring. The mixture is stirred for 5 days at room temperature and then poured into 500 mL of water. The aqueous phase is discarded and the organic phase evaporated. 7.17 g of a brown solid are then obtained (yield = 96%).

mp:115 °C (litt. = 112–114 °C , Chern S. F. Jr., *J. Org. Chem.* 1977, *42*, 178–179).

^{1}H NMR ($CDCl_3$, 400 MHz): 6.35–6.49 (m wide, 2H, NH_2); 7.50–7.60 (m, 3H, Ar-H); 7.95 (d, 7,0 Hz, 2H, Ar-H). UV-Vis (ethanol): λmax = 432 nm.

Potassium phenylazacarboxylate, RN:13444-03-6.

1 g of phenylazacarboxamide (6.7 mmol) is dissolved in a minimum of water. 2 mL of 50% potassium hydroxide are added with stirring. The mixture was irradiated by ultrasounds with an ultrasonic laboratory bath for 4 h under a nitrogen atmosphere at 20 °C. The mixture is then cooled to 0 °C and the precipitated product is recovered by filtration on a Büchner funnel. The flask is rinsed with diethyl ether. 1.02 g of a brown solid is obtained (yield = 81%). This solid decomposes quite violently at around 160 °C.

Potassium phenylazacarboxylate is stable in basic aqueous media before filtration and can be stored without decomposition in aqueous frozen form. It is sufficient to melt the medium and recover the salt by filtration just before use. In neutral or acidic media the salt decomposes at room temperature quickly with a release of gas.

3.3. Couplings

Example of coupling with 4-iodotoluene.

Conditions a: Potassium phenylazacarboxylate/R-C_6H_4-I/$Pd_2(dba)_3$/DPBS/KOH = 2/1/0.01/0.04/2 dioxane/water = 10/1, microwaves 60 °C, 6 min.

In a typical experiment potassium phenylazacarboxylate (2 mmol.), 4-iodotoluene (1 mmol,), potassium hydroxide (2.2 mmol), $Pd_2(dba)_3$ (0.01 mmol), DPBS (0.04 mmeq.) are dissolved in dioxane/water (10 mL:1 mL) under argon. The mixture is stirred and irradiated under microwaves at 60 °C for 6 min. The reaction mixture is analyzed by GC/MS. Ether extraction of the reaction mixture provides 4-methylbiphenyle.

Conditions b: Potassium phenylazacarboxylate/R-C_6H_4-I/$Pd_2(dba)_3$/HIMes,Cl/Cs_2CO_3 = 2/1/0.01/0.04/1**;** Dioxane/acetonitrile = 1/1,microwaves 60 °C, 6 min.

4. Conclusions

We have shown that arylazocarboxylates can be efficient non-organometallic arylnucleophiles in aromatic arylations. Moreover, arylazocarboxylates are stable as solid and can be easily prepared.

The coupling reactions take place in green conditions, the only by-products are nitrogen, carbon dioxyde and a potassium salt.

Author Contributions: Conceptualization, D.V.; investigation, D.V., A.J.; writing—review and editing, D.V. and N.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: The authors thank Karine Jarsalé for mass spectrometry spectra.

Conflicts of Interest: The authors declare no conflicts of interest.

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