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Palladium-Catalyzed One-Pot Synthesis of 2-Alkyl-2-arylcyanoacetates

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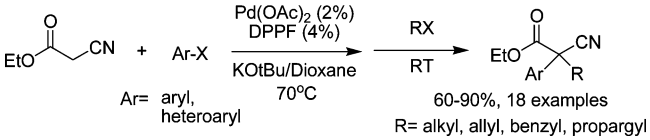
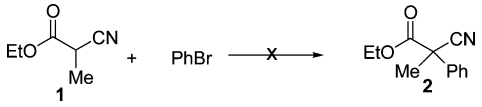


A one-pot procedure for the synthesis of 2-alkyl-2-arylcyanoacetates based on a $Pd(OAc)_2$/DPPF (DPPF = 1,1′-diphenylphosphino ferreocene)-catalyzed enolate arylation followed by in situ alkylation has been developed. This procedure tolerates a diverse range of aryl and heteroaryl bromides, and provides a rapid entry to a variety of 2-alkyl-2-arylcyanoacetates in good to excellent yield.

Aryl cyanoacetates are versatile synthons to synthesize a variety of nitrogen-containing compounds such as amino alcohols,[1] isoquinolines,[2] and β-amino acids.[3] Recent developments in the field of transition metal-catalyzed cross-coupling of enolates and aryl halides has greatly expanded the accessibility of aryl cyanoacetates.[4,5] We were interested in synthesizing a series of 2-alkyl-2-arylcyanoacetates as intermediates to support our research in medicinal chemistry. However, our initial efforts indicated that the current state-of-the-art catalyst systems were poorly applicable to our desired substrates. Specifically, copper-catalyzed systems, which are typically suitable for aryl iodide substrates, were found to be generally unsuitable for the more readily available aryl bromide substrates.[5] As for palladium catalysis, $P(t\text{-Bu})_3/Pd(dba)_2$ failed to tolerate heteroaryl halides, an important category of substrates for pharmaceutical applications.[4a,b] The cage-phosphine $P(i\text{-BuNCH}_2CH_2)_3N/Pd_2(bda)_3$ catalyst system, which has been reported to provide excellent substrate scope to include heteroaryl halides, was found to be less attractive for our specific needs.[6] Most importantly, these state-of-the-art systems failed to directly couple aryl halides with simple 2-alkylcyanoacetate, such as ethyl 2-methylcyanoacetate (**1**) (Scheme 1). Therefore, we set out to find a more general solution to this problem and herein we report our development of a one-pot, air-stable palladium-catalyzed procedure for the efficient synthesis of 2-alkyl-2-arylcyanoacetates in 60−90% yields.

SCHEME 1. Direct Arylation of 1



We first carried out a systematic screening of palladium, ligands, and base in an effort to directly couple 2-alkylcyanoacetate **1** with bromobenzene. Unfortunately, we were unsuccessful in identifying conditions to yield a detectable amount of coupling product **2**. We then took a step back and found that a catalyst system comprised of $Pd(OAc)_2$, DPPF, and KO*t*-Bu (DPPF = 1,1′-diphenylphosphino ferreocene) efficiently catalyzed reaction of unsubstituted ethyl cyanoacetate (**3**) with a wide range of aryl halides including heteroaryl bromides.[7] Since more than 2 equiv of KO*t*-Bu was present in the catalytic system,[8] we reasoned that the arylated cyanoacetate product would exist as an anion, and therefore, could be trapped by suitable alkyl electrophiles. Thus, if the palladium catalyst did not interfere with alkyl electrophiles, such as methyl iodide or allyl bromide,[9] the desired 2-alkyl-2-arylcyanoacetate could be accessed in a one-pot procedure by sequential addition of an alkylating reagent (Scheme 2).[10] We were glad to find out that this is indeed possible. Heating a mixture of **3** and phenyl bromide in the presence of $Pd(OAc)_2$ (2%), DPPF (4%), and KO*t*-Bu (2.5 equiv) in 1,4-dioxane at 70 °C for 1 h, followed by MeI (1.2 equiv) quench at room temperature cleanly afforded the desired coupling product 2-methyl-2-phenylcyanoacetate (**2**) in 88% isolated yield (Table 1, entry 2).

The general utility of one-pot sequential $Pd(OAc)_2$/DPPF-catalyzed arylation and traditional alkylation procedure for the synthesis of a range of 2-alkyl-2-arylcyanoacetates was explored.

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(1) (a) Joule, J. A. *Sci. Synth.* **2001**, *10*, 361−652. (b) Dornow, A.; Fust, K. J. *Chem. Ber.* **1954**, *87*, 985−90.

(2) For a recent example see: Frohn, M.; Burli, R. W.; Riahi, B.; Hungate, R. W. *Tetrahedron Lett.* **2007**, *48*, 487−489.

(3) (a) Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, 1−15. (b) Liu, T.-Y.; Long, J.; Li, B.-J.; Jiang, L.; Li, R.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Org. Biomol. Chem.* **2006**, *4*, 2097−2099.

(4) For Pd-catalyzed reactions, see: (a) Stauffer, S. R.; Beare, N. A.; Stambuli, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4641−4642. (b) Beare, N. A.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 541−555. (c) Tao, X.; Huang, J.; Yao, H.; Qian, Y. *J. Mol. Catal. A* **2002**, *186*, 53−56. (d) You, J.; Verkade, J. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 5051−5053. (e) You, J.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8003−8007. (f) Uno, M.; Seto, K.; Ueda, W.; Masuda, M.; Takahashi, S. *Synthesis* **1985**, 506−508.

(5) For Cu-catalyzed reactions, see: (a) Okuro, K.; Furuune, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1993**, *58*, 7606−7607. (b) Pivsa-Art, S.; Fukui, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2039−2042. (c) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem. Eur. J.* **2004**, *10*, 5607−5622. (d) Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 3534−3542.

(6) The $P(i\text{-BuNCH}_2CH_2)_3N$ ligand is a viscous and air-sensitive liquid. The bench-top handling of this ligand in air for screening and scale-up was found to be somewhat unattractive for our needs. See refs 4d,e.

(7) DPPF has been previously examined in related cross-coupling reactions, see: (a) Gao, C.; Tao, X.; Qian, Y.; Huang, J. *Synlett* **2003**, 1716−1718. (b) Mitin, A. V.; Kashin, A. N.; Beletskaya, I. P. *Russ. J. Org. Chem.* **2004**, *40*, 802−812.

(8) When 1.2 equiv of KOtBu was used, incomplete conversion of **3** was observed.

(9) Allyl groups are susceptible to palladium-catalyzed olefin isomerizations under certain conditions, see: Negishi, E.-I. *Handb. Organopalladium Chem. Org. Synth.* **2002**, *2*, 2783−2788.

(10) Use of MeI as an in situ trapping reagent has been demonstrated by Hartwig et al. in the palladium-catalyzed arylation of malonates but not cyanoacetates, see ref 4b. No other alkylating reagents have been demonstrated as in situ traps.

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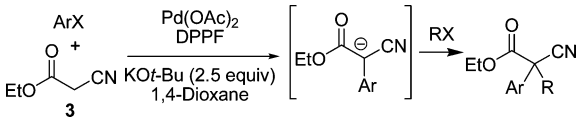
SCHEME 2. One-Pot Arylation−Alkylation of 3



The procedure was found to exhibit excellent scope (Table 1). A variety of aryl and heteroaryl bromides participated effectively in this arylation reaction. Similarly, a variety of alkyl electrophiles participated effectively in the alkylation reaction. For example, the reaction of **3** with phenyl bromide was efficiently trapped by a range of alkyl electrophiles including alkyl iodides (entry 2−3), benzyl bromide (entry 4), allyl bromide (entry 5), and propargyl bromides (entry 6−8) to afford the desired 2-alkylarylcyanoacetates in good yields. Notably, use of allyl bromide in the presence of the palladium catalyst did not result in the formation of any undesired olefin isomerized products. In addition, the $Pd(OAc)_2$/DPPF-catalyzed reaction of **3** and ortho-substituted (entries 9−11) and electron-poor aryl halides (entries 12 and 13) proceeded efficiently. These reactions could also be trapped with a range of alkyl halides to afford the desired products in good yields. Specifically, reaction of **3** with 2-bromoanisole gave 79% yield of ethyl 2-methyl-2-(2-methoxyphenyl)cyanoacetate after trapping with methyl iodide (entry 11) and reactionof 4-fluorobromobenzene gave 77% yield after trapping with benzyl bromide (entry 12).

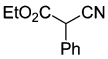
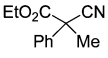
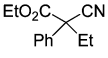
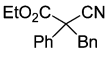
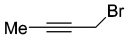
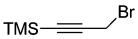
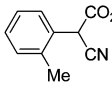
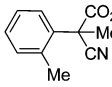
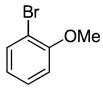
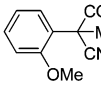
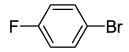
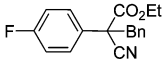
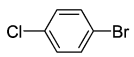
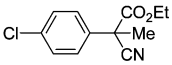
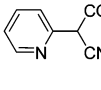
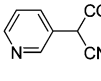
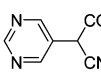
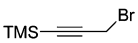
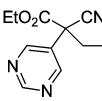
In contrast to the previously published reaction conditions with $P(t\text{-Bu})_3/Pd(dba)_2$,[4b] under which cyanoacetates failed to couple with heteroaryl halides, this $Pd(OAc)_2$/DPPF catalyst system efficiently catalyzed the arylation of **3** with heteoaryl halides. For example, under our standard conditions, 2-bromopyridine reacted smoothly with **3** to give ethyl 2-(3-pyridinyl)cyanoacetate in 84% isolated yield (entry 14) and ethyl 2-allyl-2-(2-pyridinyl)cyanoacetate in 79% isolated yield when allyl bromide (1.2 equiv) was used as a trapping reagent (entry 15). Similarly, 3-bromopyridine and 5-bromopyrimidine both reacted with **3** in high yield with or without a trapping reagent (entry 16−19).[11]

In summary, we have developed an efficient one-pot procedure for the synthesis of 2-alkyl-2-arylcyanoacetates based on a $Pd(OAc)_2$/DPPF catalytic system under basic conditions. This procedure is compatible with a wide range of arylating and alkylation reagents. Importantly, heteroaryl halides are well tolerated by this protocol. While the mechanism of this $Pd(OAc)_2$/DPPF-catalyzed arylation reaction is expected to go through similar mechanism as that of $P(t\text{-Bu})_3/Pd(dba)_2$,[4b] the enhanced reactivity of the former toward heteroaryl halides may be explained by the inability of nucleophilic nitrogens to replace bidentate phosphine ligand from palladium and such a process is facile for $P(t\text{-Bu})_3$-ligated Pd-aryl species.[12] Overall, this procedure provides a general and easy access to a variety of 2-alkyl-2-arylcyanoacetates in good yields.

Experimental Section

General Procedure for the Palladium-Catalyzed Arylation of 3 with Aryl and Heteroaryl Bromides: Ethyl 2-Phenylcyanoacetate[13] **(Table 1, entry 1):** To suspension of KO*t*-Bu (280 mg, 2.5 mmol) in 1,4-dioxane (3 mL) was added **3** (113 mg, 1.0 mmol) and bromobenzene (188 mg, 1.2 mmol) sequentially, resulting in a white suspension. A prepared solution of $Pd(OAc)_2$

TABLE 1. One-Pot Synthesis of 2-Alkyl-2-arylcyanoacetates via Pd-Catalyzed Coupling of 3 with Aryl Halides[a]

Entry	ArX	RX	Product	Yield[b]
1		none		90%
2	"	MeI		88%
3	"	EtI		80%[c]
4	"	BnBr		79%
5	"			74%
6	"			60%[d]
7	"			66%
8	"			90%[e]
9		none		90%
10	"	MeI		84%
11		MeI		79%
12		BnBr		77%
13		MeI		72%
14		None		84%
15	"			79%
16		None		85%
17	"			83%
18		None		85%
19	"			81%

[a] Reaction conditions: ethyl cyanoacetate **3**, Ar−X (1.2 equiv), $Pd(OAc)_2$ (2%), DPPF (4%), KO*t*-Bu (2.5 equiv), 70 °C (1−4 h). RX (1.2 equiv), rt/1−4 h. [b] Isolated yield. [c] EtI, 80 °C for 4 h. [d] NaH (1.1 equiv) added with propargyl bromide. [e] 1-Bromo-3-trimethylsilyl propyne, 55 °C for 12 h.

(11) In the absence of a Pd catalyst/ligand, the control experiment of 5-bromopyrimidine with **3** and KO*t*-Bu produced ~30% conversion after overnight heating, whereas 3-bromopyridine gave no detectable amount of product, indicating efficiency of Pd catalysis.

(4.5 mg, 0.02 mmol) and DPPF (23 mg, 0.04 mmol) in 1,4-dioxane (1 mL) was then added. The resulting mixture was heated at 70 °C for 1 h, when GC analysis of the reaction mixture indicated the complete consumption of **3**. The reaction was cooled to room temperature, and AcOH (1 N, 2 mL) and EtOAc (8 mL) were added sequentially. The organic layer was dried, concentrated, and chromatographed (SiO_2, hexanes → 15% EtOAc/hexanes) to give ethyl 2-phenylcyanoacetate as a colorless oil (171 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.46 (m, 5H), 4.74 (s, 1H), 4.18−4.24 (m, 2H), 1.24 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 130.1, 129.3, 129.2, 127.9, 115.8, 63.2, 43.7, 13.9.

Ethyl 2-(2-Pyridinyl)cyanoacetate[14] **(Table 1, entry 14): 3** (113 mg, 1.0 mmol) and 2-bromopyridine (190 mg, 1.2 mmol) were added sequentially to a suspension of KO*t*-Bu (280 mg, 2.5 mmol) in 1,4-dioxane (3 mL), resulting in a white suspension. A prepared solution of $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and DPPF (23 mg, 0.04 mmol) in 1,4-dioxane (1 mL) was then added. The resulting mixture was heated at 70 °C for 1 h, when GC analysis of the reaction mixture indicated complete consumption of **3**. The reaction was cooled to room temperature and AcOH (1 N, 2 mL) and methylene chloride (8 mL) were added sequentially. The organic layer was dried, concentrated, and chromatographed (SiO_2, CH_2Cl_2) to give ethyl 2-(2-pyridinyl)cyanoacetate as a yellow solid (162 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.01 (s, 1H), 7.65 (d, J = 6.0 Hz, 1H), 7.59 (t, J = 8.0 Hz, 1H), 7.30 (d, J = 9.2 Hz, 1 H), 6.67 (t, J = 6.4 Hz, 1H), 4.24 (q, J = 7.2 Hz, 2 H), 1.33 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 155.6, 139.7, 134.0, 120.4, 119.3, 112.5, 62.6, 60.2, 14.6.

General Procedure for the One-Pot Synthesis of 2-Alkyl-2-arylcyanoacetates with Aryl and Heteroaryl Bromides: Ethyl 2-Methyl-2-phenylcyanoacetate[5b] **(Table 1, entry 2):** To suspension of KO*t*-Bu (280 mg, 2.5 mmol) in 1,4-dioxane (3 mL) was added **3** (113 mg, 1.0 mmol) and bromobenzene (188 mg, 1.2 mmol) sequentially, resulting in a white suspension. A prepared solution of $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and DPPF (23 mg, 0.04 mmol) in 1,4-dioxane (1 mL) was then added. The resulting mixture was heated at 70 °C for 1 h, when GC analysis of the reaction mixture indicated the complete consumption of **3**. The reaction was cooled to room temperature, and methyl iodide (170 mg, 1.2 mmol) was added. The resulting mixture was stirred at ambient temperature for 1 h, and GC analysis indicated complete consumption of ethyl 2-phenylcyanoacetate. Hexanes (10 mL) was then added and the resulting suspension was passed through a frit. The filtrate was concentrated and column chromatographed (SiO_2, hexanes → 10% EtOAc/hexanes) to give ethyl 2-methyl-2-phenylcyanoacetate as a colorless oil (179 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52−7.54 (m, 2 H), 7.34−7.42 (m, 3 H), 4.18−4.27 (m, 2 H), 1.94 (s, 3 H), 1.23 (t, J = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 135.9, 129.2, 128.8, 125.7, 119.5, 63.2, 48.3, 24.9, 13.8.

2-Allyl-2-(2-pyridinyl)cyanoacetate (Table 1, entry 15): 3 (113 mg, 1.0 mmol) and 2-bromopyridine (190 mg, 1.2 mmol) were added sequentially to a suspension of KO*t*-Bu (280 mg, 2.5 mmol) in 1,4-dioxane (3 mL), resulting in a white suspension. A prepared solution of $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and DPPF (23 mg, 0.04 mmol) in 1,4-dioxane (1 mL) was then added. The resulting mixture was heated at 70 °C for 1 h, when GC analysis of the reaction mixture indicated the complete consumption of **3**. The reaction was cooled to room temperature, and allyl bromide (145 mg, 1.2 mmol) was added. The resulting mixture was stirred at ambient temperature for 1 h, and HPLC analysis indicated complete consumption of ethyl 2-(2-pyridinyl)cyanoacetate. Aqueous AcOH (1 N, 2 mL) and methylene chloride (8 mL) were added sequentially. The filtrate was concentrated and column chromatographed (SiO_2, 10% → 50% EtOAc/hexanes) to give ethyl 2-allyl-2-(2-pyridinyl)cyanoacetate as a pale yellow oil (191 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): 8.62 (d, J = 4.8 Hz, 1 H), 7.78 (t, J = 7.6 Hz, 1 H), 7.62 (d, J = 8.4 Hz, 1 H), 7.30−7.33 (m, 1 H), 5.73−5.83 (m, 1 H), 5.19−5.26 (m, 2 H), 4.25−4.30 (m, 2 H), 3.17 (dd, J = 7.2, 14.0 Hz, 1 H), 3.04 (dd, J = 7.2, 14.0 Hz, 1 H), 1.25 (t, J = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 152.2, 148.3, 136.0, 129.3, 122.1, 120.1, 119.6, 116.4, 61.8, 54.6, 39.3, 12.4.

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Supporting Information Available: Synthetic methods and spectral assignments and copies of ^{1}H NMR and ^{13}C NMR for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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