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Tetrahedron Letters 45 (2004) 5823–5825

Tetrahedron Letters

Synthesis of arylacetic acid derivatives from diethyl malonate using in situ formed palladium(1,3-dialkylimidazolidin-2-ylidene) catalysts

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Received 8 April 2004; revised 22 May 2004; accepted 3 June 2004

Abstract—The in situ prepared three component system $Pd(OAc)_2$/1,3-bis(alkyl) imidazolinium halide LHX (**1**–**5**)/Cs_2CO_3 catalyses the arylation of diethyl malonate efficiently with accompanying dealkoxycarbonylation. Imidazolinium salts with bulky benzyl and alkoxyethyl groups were found to be the most efficient and afforded α-arylacetates in high yields when employing a wide variety of substrates.

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Transition metal-catalyzed cross-coupling is a versatile and highly useful transformation, which yields a variety of organic compounds.[1] For example, arylation of alkenes (Mizoroki–Heck reaction),[2] arylboronic acids (Suzuki–Miyaura reaction),[3] aldeydes,[4] ketones,[5] acetates[6] and malonates[7] are very often employed. In the past few years, many attempts have been made to develop effective palladium complexes for the α-arylation of carbonyl compounds.[8] However, despite substantial improvements, significant limitations still exist. For instance, aryl chlorides containing electron-donating groups have proved problematic. Moreover, the use of Pd and phosphine ligands limit the attraction of these methods for certain applications: the phosphine ligands require air-free handling to prevent their oxidation and are comparatively difficult to make or rather expensive to purchase.

Arylacetic acid derivatives are important structural units frequently found in analgesics and antiinflammatory drugs.[9] Various approaches have been studied for the synthesis of α-aryl acetates using coupling reactions and recently significant progress has been made involving the direct introduction of an acetic acid ester moiety into an aromatic ring using palladium-catalyzed reactions.[6a]

In one approach, a convenient synthesis developed by Kondo et al. involved the $Pd_2(dba)_3/PBu^t_3$ mediated coupling of diethyl malonate with aryl iodides or bromides at 120 °C in the presence of 10 equiv of Cs_2CO_3 and gave fair to good yields.[10] In this area, aryl chlorides, which are the most attractive class of substrate due to their low cost and ready availability, have not exhibited noteworthy reactivity. Thus, it is desirable to find less costly alternatives and/or operationally simple procedures.

It has been previously disclosed that *N*-heterocyclic carbene (NHC) ligands serve as excellent supporting ligands in the Pd-catalyzed arylation and olefination of aryl halides.[11–13] It is worth noting that 'in situ' formation of the NHC complex by deprotonation of the imidazol(in)ium salt led to significantly better results than the use of the preformed complex. The success of these processes as well as the recent report by Kondo et al.[10] prompted us to examine whether in situ generated NHC ligands could be used for other C–C bond forming reactions. Herein, we report a mild, practical, Pd-catalyzed arylation of malonates using air-stable $Pd(OAc)_2$ as the catalyst, 1,3-bis(alkyl) imidazolinium halides (LHX) as the NHC ligand precursor, Cs_2CO_3 as the base and dioxane as the solvent; the reactions can be

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Keywords: Arylations; Palladium catalysts; NHC complexes; Diethyl malonate.

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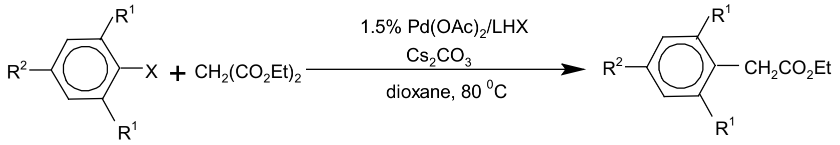
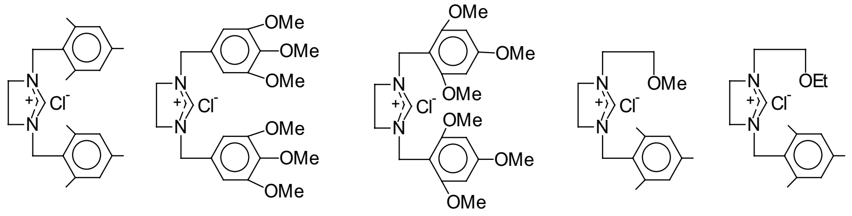
0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.06.012



Scheme 1.



1 2 3 4 5

Scheme 2. Imidazolinium salts (LHX) used.

performed without protection from air or moisture (Scheme 1). 1,3-Bis(alkyl)imidazolinium chlorides, LHX (Scheme 2, **1**–**5**) were prepared according to the literature.[14]

Table 1 summarizes our results from screening the five imidazolinium salts LHX, for a variety of substrates that undergo arylation accompanied by decarboxylation to form arylacetic acid esters. Several trends are readily apparent. Firstly, the use of saturated NHC ligand precursors (**1**–**5**) allowed lower reaction temperatures (80 °C), shorter reaction times and lower base loadings than previous work using $Pd_2(dba)_3/PBu^t_3$ as catalyst.

The procedure is simple and does not require induction periods. Secondly, the scope of this reaction is broad and includes aryl chlorides that are activated or deactivated and 2,6-disubstituted aryl bromide (entries 36–40). Thirdly, all complexes led to good conversions at low catalyst concentration (1.5 mol %). Although not dramatic, consistent differences in yields were observed in the reactions according to the ligand precursors **1**–**5**.

Table 1. Arylation of diethyl malonate catalyzed by $Pd(OAc)_2$/LHX (**1**–**5**)/Cs_2CO_3[a]

Entry	R^1	R^2	X	LHX	Time (h)	Yield (%)[b,c,d]
1	H	H	I	**1**	24	93
2	H	H	I	**2**	24	91
3	H	H	I	**3**	24	89
4	H	H	I	**4**	24	96
5	H	H	I	**5**	24	95
6	H	COMe	Br	**1**	24	89
7	H	COMe	Br	**2**	24	87
8	H	COMe	Br	**3**	24	86
9	H	COMe	Br	**4**	24	91
10	H	COMe	Br	**5**	24	89
11	H	NO_2	Br	**1**	24	87
12	H	NO_2	Br	**2**	24	85
13	H	NO_2	Br	**3**	24	83
14	H	NO_2	Br	**4**	24	89
15	H	NO_2	Br	**5**	24	88
16	H	CHO	Br	**1**	24	90
17	H	CHO	Br	**2**	24	88
18	H	CHO	Br	**3**	24	87
19	H	CHO	Br	**4**	24	94
20	H	CHO	Br	**5**	24	91
21	H	H	Br	**1**	48	85
22	H	H	Br	**2**	48	83
23	H	H	Br	**3**	48	81
24	H	H	Br	**4**	48	87
25	H	H	Br	**5**	48	84

Table 1 (*continued*)

Entry	R^1	R^2	X	LHX	Time (h)	Yield (%)[b,c,d]
26	H	COMe	Cl	**1**	24	92
27	H	COMe	Cl	**2**	24	89
28	H	COMe	Cl	**3**	24	85
29	H	COMe	Cl	**4**	24	93
30	H	COMe	Cl	**5**	24	90
31	H	OMe	Cl	**1**	24	85
32	H	OMe	Cl	**2**	24	83
33	H	OMe	Cl	**3**	24	81
34	H	OMe	Cl	**4**	24	87
35	H	OMe	Cl	**5**	24	84
36	Me	Me	Br	**1**	24	85
37	Me	Me	Br	**2**	24	83
38	Me	Me	Br	**3**	24	89
39	Me	Me	Br	**4**	24	91
40	Me	Me	Br	**5**	24	95

[a] Reaction conditions: 1.0 mmol of ArX, 1.0 mmol diethyl malonate, 2 mmol Cs_2CO_3, 1.5 mol% $Pd(OAc)_2$, 3 mol% LHX, dioxane (3 mL).

[b] Purity of compounds was determined by NMR and yields were based on aryl halides.

[c] All reactions were monitored by TLC.

[d] Temperature 80 °C; reaction times were not optimized.

Presumably, the bulkier and potentially hemilabile ligands derived from **4** and **5** are more effective in stabilizing the Pd complex. Bis(trimethoxybenzyl) substituted precursors such as **2** and **3** gave relatively poor yields compared with **1**, **4** and **5**. Control experiments revealed that no reaction was observed in the absence of the NHC ligand precursors.

In conclusion, five imidazolinium salts, LHX, as precursors of 1,3-dialkyl substituted NHC ligands were evaluated in Pd-catalyzed cross-coupling reactions of aryl halides with diethyl malonate with accompanying dealkoxycarbonylation. The reaction was found to proceed with high conversion (up to 96%) in relatively short reaction times and at low temperatures to give the desired arylacetic esters. It is also possible to run the reaction catalytically under an oxygen atmosphere without significant loss of yield.

Acknowledgements

We thank the Technological and Scientific Research Council of Türkiye TÜBİTAK (TÜBİTAK COST D17) and Inönü University Research Fund (BAP 2002/23) for financial support of this work.

References and notes

1. (a) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E. I., Ed.; Wiley: New York, 2002; Vol. 1; (b) Miyaruna, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
2. (a) Litke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211; (b) McGuinness, D. S.; Cavell, K. J. *Organometallics* **2000**, *19*, 741–748; (c) Zapf, A.; Beller, M. *Chem. Eur. J.* **2001**, *7*, 2908–2915.
3. (a) Mathews, C. J.; Smith, P. J.; Welton, T. *J. Mol. Catal. A: Chem.* **2003**, *206*, 77–82; (b) Heiden, M.; Pleino, H. *Chem. Eur. J.* **2004**, *10*, 1789–1797; (c) Walker, S. D.; Barder, T. I.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871–1876.
4. Terao, Y.; Fukuoka, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2002**, *43*, 101–104.
5. (a) Gaertzen, O.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 465–475; (b) Lee, S.; Beare, N. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 8410–8411.
6. (a) Jorgensen, M.; Lee, S.; Liu, X.; Wokowski, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 12557–12565; (b) Moradi, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7996–8002.
7. (a) Beare, N. A.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 541–555; (b) Wokowski, J. P.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 4289–4291.
8. (a) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234–245; (b) Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 953–956.
9. Dannhardt, G.; Kiefer, W. *Eur. J. Med. Chem.* **2001**, *36*, 109–126.
10. Kondo, Y.; Inamoto, K.; Uchiyama, M.; Sakamoto, T. *Chem. Commun.* **2001**, 2704–2705.
11. (a) Böhm, V. P. W.; Gstöttmayr, C. W. K.; Weskamp, T.; Herrmann, W. A. *J. Organomet. Chem.* **2000**, *595*, 186–190; (b) Fürstner, A.; Leitner, A. *Synlett* **2001**, 290–292.
12. Gürbüz, N.; Özdemir, I.; Demir, S.; Çetinkaya, B. *J. Mol. Catal. A: Chem.* **2004**, *209*, 23–28.
13. (a) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *Organometallics* **2002**, *21*, 2866–2873; (b) Grasa, G. A.; Viciu, M. S.; Huang, J.; Zhang, C.; Trudell, M. L.; Nolan, S. P. *Organometallics* **2002**, *21*, 2866–2873.
14. (a) Saba, S.; Brescia, A.; Kaloustian, M. K. *Tetrahedron Lett.* **1991**, *32*, 5031–5034; (b) Çetinkaya, E.; Hitchcock, P. B.; Jasim, H. A.; Lappert, M. F.; Spyropoulos, K. *J. Chem. Soc., Perkin Trans. 1* **1992**, 561–567.