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A General and Mild Copper-Catalyzed Arylation of Diethyl Malonate

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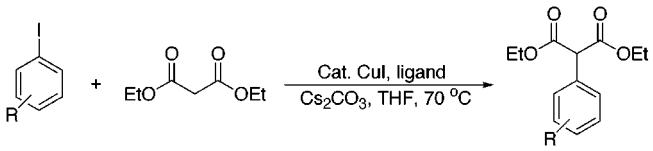
ABSTRACT



A general method for the synthesis of α-aryl malonates is described. The coupling of an aryl iodide and diethyl malonate in the presence of Cs_2CO_3 and catalytic amounts of copper(I) iodide and 2-phenylphenol affords the α-aryl malonate in good to excellent yields. The mild reaction conditions and high levels of functional group compatibility make this an attractive synthetic alternative to previous methods.

α-Aryl carboxylic acids and acid derivatives comprise an important class of organic molecules. Aside from their prevalence in numerous natural products,[1] they have been widely used in pharmaceutical applications. Indeed, α-aryl acetic acids (e.g., indomethacin, sulindac, ibufenac, diclofenac) and α-aryl propionic acids (e.g., ibuprofen, naproxen, ketoprofen) are two of the main classes of nonsteroidal antiinflammatory drugs (NSAIDs).[2]

α-Substituted carboxylic acids can be accessed by a number of synthetic methods. Of these, the alkylation of esters of malonic acid followed by hydrolysis and decarboxylation was for years the most effective, as a result of the relatively high acidity of the α-protons.[3] While the advent of strong, hindered bases (e.g., LDA, NaHMDS) has obviated the need to use β-dicarbonyl compounds to generate enolates, the classical malonate alkylation is still an important synthetic tool. The arylation of malonates is, however, less straightforward. α-Aryl malonates have enormous potential in the synthesis of α-aryl acids and have themselves recently been reported to be effective modulators of Ca^{2+}-activated K^+ channels in mammalian cell membranes.[4] Therefore, an effective and reliable method for their synthesis is desirable.

Among the many methods available for the synthesis of α-aryl carbonyl compounds, a great deal of recent attention has focused on the development of the palladium-catalyzed coupling of enolates with aryl halides. Research efforts in several laboratories (including our own) have led to effective methods for the synthesis of α-aryl ketones,[5] amides,[6] and esters.[7] While there have been several reports of palladium-catalyzed coupling of an aryl halide with the enolate of a malonate ester,[5g,h,8] these systems do not work in the presence of certain aromatic moieties (e.g., $ArNH_2$, ArOH, ArN(H)COR).

(1) Select examples. (a) Vancomycin: Sheldrick, G. M.; Jones, P. G.; Kennard, O.; Williams, D. H.; Smith, G. A. *Nature* **1978**, *271*, 223. (b) Lucuminic acid: Takeda, T.; Gonda, R.; Hatano, K. *Chem. Pharm. Bull.* **1997**, *45*, 697. (c) Polymastiamide A: Kong, F.; Andersen, R. J. *J. Org. Chem.* **1993**, *58*, 6924. (d) Chloropeptin I and II: Hegde, V. R.; Dai, P.; Patel, M.; Gullo, V. P. *Tetrahedron Lett.* **1998**, *39*, 5683. (e) Vulculic acid: Kimura, Y.; Nishibe, M.; Nakajima, H.; Hamasaki, T. *Agric. Biol. Chem.* **1991**, *55*, 1137.

(2) Rieu, J.-P.; Boucherle, A.; Cousse, H.; Mouzin, G. *Tetrahedron* **1986**, *42*, 4095.

(3) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry Part B: Reactions and Synthesis*; Plenum Press: New York, 1990; pp 13−16.

(4) Beyer, J.; Jensen, B. S.; Strøbæk, D.; Christophersen, P.; Teuber, L. WO Patent 00/37422, 2000.

(5) (a) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108. (b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382. (c) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740. (d) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7581. (e) Åhman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918. (f) Satoh, T.; Kametani, Y.; Terao, Y.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1999**, *40*, 5345. (g) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473. (h) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360.

(6) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546.

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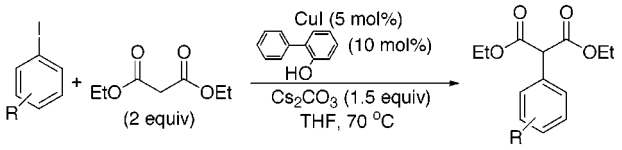
In recent years, we have developed copper-catalyzed methods for the arylation of amides,[9] amines,[9,10] nitrogen-containing heterocycles,[9,11] hydrazides,[9,12] and phenols.[13] The arylation of activated methylene compounds mediated by copper salts is a well-established process, dating back to the development of the Hurtley reaction in 1929.[14] There have since been numerous reports of variants of this process,[15] but in general high yields are only obtained with aryl halides bearing electron-withdrawing groups or *ortho* substituents capable of coordinating to copper. These reactions are usually run in nonvolatile and/or highly toxic solvents (e.g., DMSO or HMPA). Furthermore, it is often necessary to prepare the enolate (by deprotonation of the malonate using sodium hydride or a sodium alkoxide) prior to coupling. Perhaps least attractive is that in nearly all cases stoichiometric or even excess amounts of copper salts must be used. In 1993, Miura et al. reported a copper-catalyzed arylation of malonitrile, ethyl cyanoacetate, and acetylacetone using unhindered aryl iodides.[16] However, their system requires harsh conditions (DMSO, 120 °C) under which malonate esters are prone to decomposition (via ester hydrolysis and subsequent rapid decarboxylation). Konopelski and co-workers have recently developed a copper-catalyzed malonate arylation,[17] but the substrate scope is limited (only *o*-halophenols and *o*-haloanisoles are reactive) and the air-sensitive CuBr must be used. To date, therefore, there have been no general methods affording α-aryl malonates that employ catalytic amounts of copper. Because of the potential of such compounds as important synthetic intermediates and therapeutic agents, we set out to develop a general and mild catalytic method that would provide ready access to a wide variety of α-aryl diesters that could be further manipulated to a myriad of desirable products.

An important initial goal of our investigations was to find a base other than sodium hydride (or alkoxide) that would effect the desired reaction. Soluble organic bases such as triethylamine, *N*-ethyldiisopropylamine (Hunig's base), and DBU (diazabicyclo[5.4.0]undec-7-ene) completely inhibit the reaction, likely by saturating the coordination sphere of copper.[18] Upon screening commonly used inorganic bases, it was found that the use of Cs_2CO_3 is crucial to the success of the reaction. K_3PO_4 was considerably less effective, while K_2CO_3 and Na_2CO_3 did not afford any reaction at all.

With the best base determined, the effects of various additives to the reaction were surveyed. Among the effective ligands discovered, we found that phenols expedite the reaction and in general allow for the lower reaction temperatures required to circumvent excessive product decomposition. The use of phenol itself resulted in a significant amount of diaryl ether formation,[13] while phenols bearing large *ortho* substituents (^{t}Bu, ^{i}Pr) slowed the malonate arylation reaction considerably. It was found that 2-phenylphenol (*o*-hydroxybiphenyl) does not hinder the desired reaction from proceeding, but C−O bond formation occurs to only a very small extent. Furthermore, from a practical standpoint, 2-phenylphenol is a practically odorless, crystalline solid that is considerably less toxic than most other phenols. In fact, its sodium salt has been used as a preservative for citrus fruits for decades,[19] and thus it is extremely inexpensive and available from a plethora of commercial sources.

By heating a mixture of aryl iodide, Cs_2CO_3, and diethyl malonate in THF (70 °C) in the presence of catalytic amounts of copper(I) iodide and 2-phenylphenol under an inert atmosphere (Scheme 1), the corresponding α-aryl malonate

Scheme 1. Arylation of Diethyl Malonate



can be obtained in good to excellent yields (Table 1). A 2-fold excess of diethyl malonate (relative to iodide) is necessary to drive the reaction to completion in a reasonable amount of time. We found that this reaction can be run at higher temperatures using only a slight excess of malonate; however, these reaction conditions lead to unacceptable amounts (typically ∼10%) of the decarboxylated product.

The malonate arylation proceeds smoothly using a diverse array of aryl iodides, including electron-rich (entry 8) and heterocyclic (entry 6). Even the sterically hindered 2-iodoisopropylbenzene (entry 4) can be converted to the desired product, although 10 mol % CuI and 15 mol % 2-phenylphenol are required to facilitate complete conversion. Importantly, palladium-incompatible functional groups are well

(7) (a) Fauvarque, J. F.; Jutand, A. *J. Organomet. Chem.* **1979**, *177*, 273. (b) Carfagna, C.; Musco, A.; Sallese, G.; Santi, R.; Fiorani, T. *J. Org. Chem.* **1991**, *56*, 261. (c) Galarini, R.; Musco, A.; Pontellini, R.; Santi, R. *J. Mol. Catal.* **1992**, *72*, L11. (d) Sakamoto, T.; Kondo, Y.; Masumoto, K.; Yamanaka, H. *Heterocycles* **1993**, *36*, 2509. (e) Sakamoto, T.; Kondo, Y.; Masumoto, K.; Yamanaka, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 235. (f) Terao, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1998**, *39*, 6203. (g) Agnelli, F.; Sulikowski, G. A. *Tetrahedron Lett.* **1998**, *39*, 8807. (h) Moradi, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.*, **2001**, *123*, 7996. (i) Lee, S.; Beare, N. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 8410.

(8) (a) Ciufolini, M. A.; Qi, H.-B.; Browne, M. E. *J. Org. Chem.* **1988**, *53*, 4151. (b) Djakovitch, L.; Köhler, K. *J. Organomet. Chem.* **2000**, *606*, 101.

(9) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727.

(10) Antilla, J. C.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 2077.

(11) Kiyomori, A.; Marcoux, J.-F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657.

(12) Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803.

(13) Marcoux, J.-F.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539.

(14) Lindley, J. *Tetrahedron* **1984**, *40*, 1433 and references therein.

(15) (a) Setsune, J.; Matsukawa, K.; Wakemoto, H.; Kitao, T. *Chem. Lett*. **1981**, 367. (b) Setsune, J.; Matsukawa, K.; Kitao, T. *Tetrahedron Lett.* **1982**, *23*, 663. (c) Osuka, A.; Kobayashi, T.; Suzuki, H. *Synthesis* **1983**, 67. (d) Setsune, J.; Ueda, T.; Shikata, K.; Matsukawa, K.; Iida, T.; Kitao, T. *Tetrahedron* **1986**, *42*, 2647. (e) Ugo, R.; Nardi, P.; Psaro, R.; Roberto, D. *Gazz. Chim. Ital.* **1992**, *122*, 511. (f) Pivsa-Art, S.; Fukui, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2039.

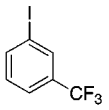
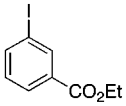
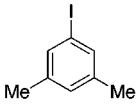
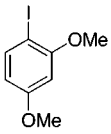
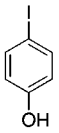
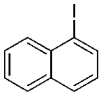
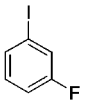
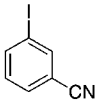
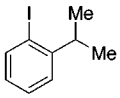
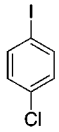
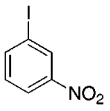
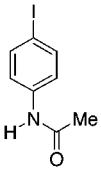
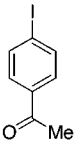
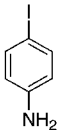
(16) Okuro, K.; Furuune, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1993**, *58*, 7606.

(17) (a) Konopelski, J. P.; Hottenroth, J. M.; Oltra, H. M.; Véliz, E. A.; Yang, Z.-C. *Synlett* **1996**, 609. (b) Hang, H. C.; Drotleff, E.; Elliott, G. I.; Ritsema, T. A.; Konopelski, J. P. *Synthesis* **1999**, 398.

(18) Miura has made a similar observation in his system; see ref 16.

(19) Johnson, G. D.; Harsy, S. G.; Geronimo, J.; Wise, J. M. *J. Agric. Food. Chem.* **2001**, *49*, 2497.

Table 1. Copper-Catalyzed Arylation of Diethyl Malonate[a]

entry	iodide	time	yield[b]	entry	iodide	time	yield[b]	entry	iodide	time	yield[b]
1		24 h	91%	7		24 h	89%	12		24 h	86%
2		27 h	95%	8		30 h	90%	13		29 h	80%[e]
3		30 h	98%	9		24 h	87%	14		24 h	61%
4		31 h	84%[c]								
5		24 h	94%	10		24 h	84%	15		29 h	75%[f]
6		26.5 h	73%[d]	11		24 h	86%	16		29 h	70%

[a] Reaction conditions: 1 equiv of aryl iodide, 2 equiv of diethyl malonate, 1.5 equiv of Cs_2CO_3, 5 mol % CuI, 10 mol % 2-phenylphenol, THF (1 M in aryl iodide), under argon at 70 °C for indicated time. [b] Isolated yields are the average of two runs and are estimated to be >95% pure by ^{1}H NMR and GC analysis. All previously unknown compounds gave satisfactory ^{1}H NMR, ^{13}C NMR, IR, and combustion analysis data. [c] Using 10 mol % CuI and 15 mol % 2-phenylphenol. [d] Reaction went to only 90% conversion in indicated time. [e] Using 3 equiv diethyl malonate and 3.5 equiv Cs_2CO_3. [f] Using 3 equiv diethyl malonate and 2.5 equiv Cs_2CO_3.

tolerated (entries 13, 15, and 16).[20] The method is not without its drawbacks, however. Aryl bromides are essentially unreactive under these conditions.[21] Additionally, substrates containing certain functional groups in the *ortho* position (e.g., $-NO_2$, $-OH$, $-NH_2$) are problematic, possibly because an unreactive copper complex is formed. Furthermore, in select cases, ligand arylation competes with the desired reaction thereby decreasing the overall yield.[13] Lastly, product decomposition (to give the α-aryl acetate) is not completely inhibited, with products having electron-withdrawing substituents on the aromatic ring being more prone to decarboxylation.[22]

It is unclear as to exactly what role the phenol ligand plays in the reaction.[23] It is likely that the catalytically active species is a copper(I) enolate, as proposed by Setsune.[15a,b,d] When the optimized reaction conditions were applied to the attempted arylation of the cyclic isopropylidene malonate (Meldrum's acid, Figure 1), 1,3-cyclopentanedione, and 1,3-cyclohexanedione, no desired products were observed. This suggests that a bidentate binding of the enolate through the oxygen atoms (Figure 2) to copper is required.

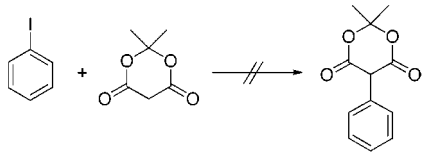


Figure 1. Attempted arylation of Meldrum's acid.

Di-*tert*-butyl malonate is reactive under these conditions, albeit to a much lesser extent than the diethyl ester (possibly

(20) We found that the yields were slightly higher in entries 13 and 15 when 3 equiv of malonate was used to suppress competing processes, presumably carbon−heteroatom bond formation.

(21) The use of bromobenzene in place of iodobenzene afforded only trace amounts (<2%) of the α-aryl malonate.

(22) Even in these cases, though, there is usually less than 10% decarboxylation.

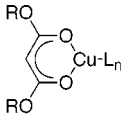


Figure 2. Required bidentate binding of copper enolate.

as a result of steric hindrance). Surprisingly, dimethyl malonate was also less reactive; this may be due to decreased solubility of the copper enolate.

In conclusion, we have developed a mild, general catalytic system for the synthesis of α-aryl malonates.[24] Aryl iodides bearing a variety of functional groups can be effectively coupled to diethyl malonate in high yields using inexpensive and widely available reagents, making this a superior method to those described previously. Future work will focus on gaining a better understanding of the reaction mechanism in addition to expanding the substrate scope to include aryl bromides and other enolates.

(23) In the absence of 2-phenylphenol, the arylation of iodobenzene under the aforementioned reaction conditions proceeded to only ~80% conversion.

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Supporting Information Available: Experimental details and characterization data for all unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) **General Procedure for Malonate Arylation.** An oven-dried Schlenk tube equipped with a magnetic stirbar and a Teflon stopcock was evacuated while hot and allowed to cool under argon. The tube was charged sequentially with CuI (5 mol %), 2-phenylphenol (10 mol %), Cs_2CO_3 (1.5 mmol), and the aryl iodide (1.0 mmol), if a solid. The tube was evacuated and backfilled with argon (3 times), and the Teflon stopcock was replaced with a rubber septum. The aryl iodide (if a liquid) was added volumetrically (1.0 mmol), followed by diethyl malonate (2.0 mmol) and anhydrous THF (1.0 mL). The septum was replaced by the Teflon stopcock under a positive pressure of argon, and the sealed tube was placed in an oil bath preheated to 70 °C. After the designated time period, the reaction was allowed to cool to room temperature and was then partitioned between ethyl acetate (20 mL) and saturated aqueous NH_4Cl (10 mL). The organic portion was dried (Na_2SO_4), filtered through a plug of Celite, and concentrated on a rotary evaporator. The material thus obtained was purified by silica gel chromatography to give the product α-aryl malonate.