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Expedient synthesis of novel β-ketoesters from the Mizoroki–Heck coupling of ethyl 3-ethoxyacrylate with aryl and pyridyl halides

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ABSTRACT

It is well known that β-ketoesters are useful intermediates for the synthesis of a range of heterocyclic templates. While there are many useful synthetic methods available to access these intermediates, there are still opportunities for the discovery of useful methodologies for their construction from novel starting materials. In this regard, we report on the discovery of a facile Pd-catalyzed Mizoroki–Heck coupling of ethyl 3-ethoxyacrylate with aryl and heteroaryl halides to form substituted alkoxyacrylates which can be hydrolyzed to form novel aryl and heteroaryl β-ketoesters.

Alkyl, aryl, and heteroaryl β-ketoesters are key intermediates in organic syntheses and often serve as intermediates for the formation of a wide range of heterocycles including substituted thiouracils, uracils, pyrroles, indoles, pyrazoles, pyridines, coumarins, and fused ring systems.[1] Many general routes have been developed for the synthesis of β-ketoesters including the classical Claisen, Dieckmann, and Blaise syntheses.[2,3] Also, diverse aryl and heteroaryl β-ketoesters can be made readily from aryl or heteroaryl carboxylic acids,[4] aldehydes,[5] acid chlorides,[6] and methyl ketones[7] or via carbonylation of aryl halides with palladium catalysis.[8] While these methods are of great utility, we sought to increase the diversity of the aryl and heteroaryl β-ketoesters for use in our medicinal chemistry programs by exploring their formation from the coupling of aryl/heteroaryl halides and alkoxyacrylates via Heck–Mizoroki coupling chemistry followed by an acid catalyzed hydrolysis (Fig. 1).

The use of substituted vinyl ethers or esters in the Mizoroki–Heck reaction with aromatic halides has proven to be a useful method for the synthesis of aromatic ketones and esters respectively and has attracted much synthetic attention.[9] Interestingly, we were surprised to find that the use of this methodology was typically not employed for the formation of β-ketoesters. We are aware of only two reported studies of the coupling of aryl halides with alkoxyacrylates to form vinyl alkoxide intermediates **2** that could lead to β-ketoesters **3**. First, Yamanaka et al. reported that ethyl 3-ethyoxyacrylate **1** participated in Mizoroki–Heck cross-coupling reactions with aryl and pyridyl iodides under relatively harsh, ligandless conditions (Scheme 1).[10] Secondly, Doucet reported an improved Mizoroki–Heck coupling with three aryl bromides and methyl 3-methoxyacrylate **6** mediated by the tetraphosphine ligand Tedicyp **7** to provide β-alkoxyacrylates which were subsequently converted into β-ketoesters via acid catalyzed hydrolysis (Scheme 2).[11a] While the use of Tedicyp as a ligand was of interest, it is not commercially available and requires a seven-step synthesis for its preparation.[11b] Here-in, we

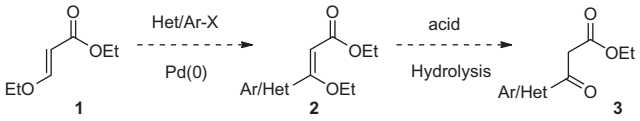
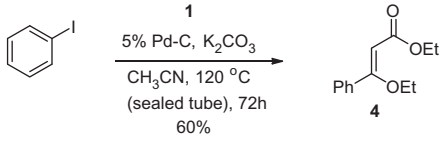


Figure 1. General Mizoroki–Heck scheme for the preparation of β-ketoesters.



Scheme 1. Yamanaka synthesis of 3,3-disubstituted ethoxyacrylates.

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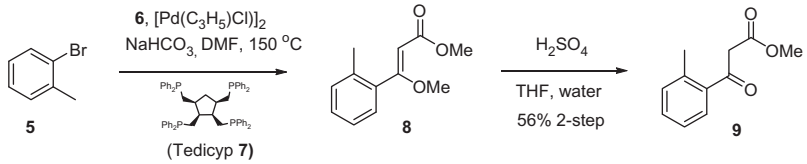
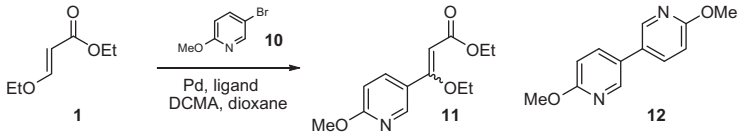


Scheme 2. Doucet synthesis of aryl β-ketoesters.

Table 1
Mizoroki–Heck coupling with trialkylphosphine ligands

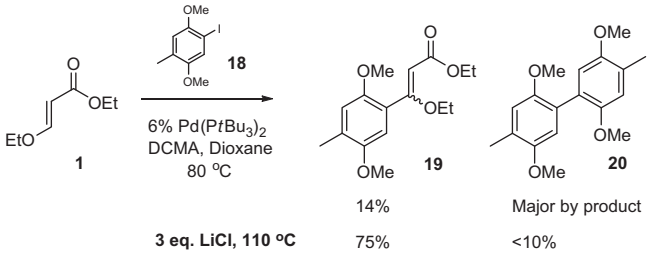


Catalyst/ligand	Temp °C/time	% **11**	% **12**
$Pd_2(dba)_3$, $HP(tBu)_3BF_4$ **13**	80, 6 h	36	
$PdP(tBu)_3$-Br dimer **14**	80, 16 h	64	
$Pd(P(tBu)_3)_2$ **15**	80, 2.5 h	82	10

report the improvement of this chemistry to afford a variety of aryl and pyridyl β-ketoesters using a commercially available, catalytic system under mild conditions for the Mizoroki–Heck coupling of ethyl 3-ethoxyacrylate **1** with aryl and pyridyl halides followed by subsequent hydrolysis.

In our initial studies of Mizoroki–Heck coupling reactions, 2-methoxy-5-bromopyridine **10** and ethyl 3-ethoxyacrylate **1** were utilized as starting materials. A screen of commercially available palladium catalysts, ligands, bases, and solvents revealed that a combination of Fu-type trialkylphosphines **13**–**15** and the base dicyclohexylmethylamine (DCMA) in dioxane were the key to effecting this coupling to provide acrylate **11** (Table 1).[12] While three different trialkylphosine ligands were successful, the bis-(tri-*t*-butyl)phosphine palladium(0) complex **15** provided the best overall yield and fastest reaction. This catalyst system is also operationally convenient due to its air stability, as opposed to the significantly less stable Pd(I) dimer **14** which also gave high yields in the Mizoroki–Heck coupling.[13] One drawback to using the bis-(tri-*t*-butylphoshine) palladium(0) **15** was the formation of the homocoupled, pyridine-dimer **12**. This byproduct was not detected with the other tri-(*t*-butyl)phosphine ligand systems. Finally, hydrolysis of the enol ether **11** with aqueous HCl in dichloromethane provided the ketoester **16** in high yield as a mixture with its enol tautomer **17** (Scheme 3).[14]

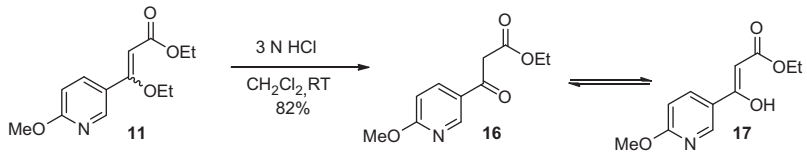
Having identified high yielding, mild conditions utilizing catalyst **15**, we examined the scope of this system with additional heteroaryl and aryl halides. Aryl iodide **18** was selected as a more difficult case and indeed proved to be problematic. Utilizing conditions developed for **10**, only 14% of **19** was isolated while the major reaction product was the homo-coupled biaryl **20** (Scheme 4). Increasing the reaction temperature from 80 °C to 110 °C and increasing the amount of **1** from 1 to 3 equiv improved the yield of **19** to 50%. Addition of lithium chloride further increased the



Scheme 4. Enhancement of the Mizoroki–Heck coupling via lithium chloride addition.

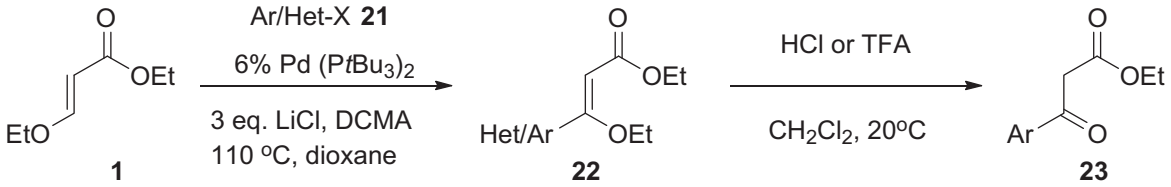
yield of **19** to 75%. Lithium chloride is known to improve some problematic Mizoroki–Heck reactions in which it is speculated that the chloride ion may displace the iodide in the oxidative addition complex (Ar–Pd–I) resulting in a highly active Ar–Pd–Cl intermediate which may accelerate subsequent steps in the catalytic cycle.[15]

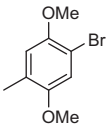
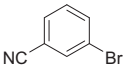
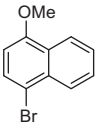
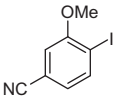
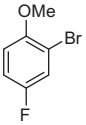
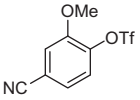
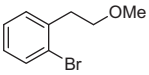
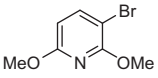
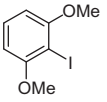
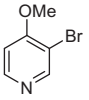
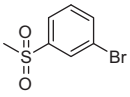
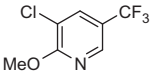
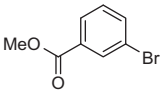
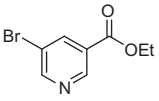
With the addition of lithium chloride, several arrays were run to test the scope of the modified Mizoroki–Heck coupling conditions with aryl and heteroaryl halides (Table 2). Since each reaction was run as part of an array, nothing was done to optimize the individual reactions except to monitor the consumption of starting halide. The results from these arrays showed that the catalyst system tolerates a range of aromatic and pyridyl halides (Table 2). Similarly to iodide **18**, bromide **21a** coupled under these conditions to give **22a** in high yields. Other electron rich aryl halides also performed well to give the desired aryl–alkyoxy acrylates **22b**–**22d**, but the sterically hindered 2,6-dimethoxylbenzene **22e** was formed in a moderate 57% yield. Electron deficient aryl-halides were also demonstrated to couple under these conditions, but generally with lower yields. While 3-ester **21g** and 3-methylsulfone **21f** formed the desired product in good yields, the 3-cyano **21h** afforded the



Scheme 3. Hydrolysis of 3,3-disubstituted acrylate to form a β-ketoester.

Table 2
Mizoroki-Heck coupling and hydrolysis reactions



	21	% Yield 22	% Yield[a] 23		21	% Yield 22	% Yield[a] 23
a		80	ND	**h**		16	ND
b		93	84	**i**		76	88[b]
c		92	91[c]	**j**		30	86[b]
d		77	91[b]	**k**		93	97, 98[b]
e		57	71	**l**		46	36
f		52	82	**m**		27[d], 56	56, 54[b]
g		71	85[b]	**n**		35	81[e]

ND—not determined.
[a] All yields are for 3 N HCl, CH_2Cl_2 except where listed.
[b] 10% TFA, CH_2Cl_2.
[c] 6 N HCl, DCE.
[d] No LiCl added to the reaction.
[e] 100% TFA.

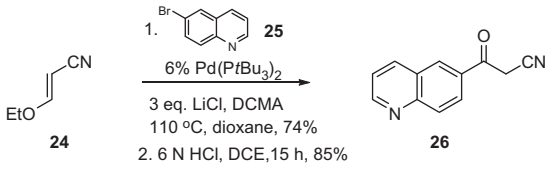
product in 16% yield. The coupling of aryl iodides containing an *ortho*-electron withdrawing group only returned recovered starting material with no observable formation of product. Not all cyano-aryl halides performed poorly in this reaction as **21i** produced the product in high yield. Interestingly, the triflate analog **21j** also delivered the desired product, but in a much lower yield.

Next, investigating heterocyclic halides in this protocol demonstrated that 3-halo-pyridines provided the highest yields of coupling products as exemplified by **21k** and **21l**. The coupling of 3-chloropyridine **21m** afforded the product **22m** in moderate yield. Initially, this reaction was run without lithium chloride and resulted in a much lower yield of product. We note that under these conditions **21m** may be a special case due to activation by the trifluoromethyl group, as other aryl chlorides and 2-chloropyridines did not form the desired coupled products under these conditions. Lastly, pyridine **21n** coupled in a modest yield under these conditions illustrating limitations on the efficiency of this methodology with this electron deficient substrate class.

Finally, depending on the halide starting material, the alkene product **22** exhibited different ratios of *E* and *Z*-isomers. There was no attempt to isolate and specifically characterize each isomer; instead, the isomer mixture was hydrolyzed to the β-ketoester **23**. Initially, a mixture of 3.0 N aqueous hydrochloric acid and dichloromethane was employed (Table 2);[15] however, some alkene products underwent hydrolysis slowly in the bi-phasic mixture. In these cases, the rate of hydrolysis could be increased, and the reaction pushed to completion via the use of 6 N HCl and dichloroethane (DCE) as in **23c** or by switching to 10% trifluoroacetic acid in dichloromethane as exemplified by examples **23d**, **23g**, **23j**, and **23k** or 100% trifluoroacetic acid for **21n**.[16]

Typically, these Heck coupling reactions were run under anaerobic conditions in sealed reaction vials. While this was fine for small scale array reactions, it could be quite cumbersome for larger scale work. Further examination of the coupling conditions demonstrated that the reaction could be scaled in good yields on a multi-gram scale in a standard round bottom flask and condenser as exemplified in **22c** (7.7 mmol, 92%).[17,18]

Finally, in one case we examined this protocol for the formation of a β-ketonitrile. Accordingly, *trans*-3-ethoxyacrylonitrile **24** and 6-bromoquinoline **25** coupled to give the desired alkene products



Scheme 5. Mizoroki–Heck coupling for the formation of a β-ketonitrile.

in moderate yield. Standard hydrolysis with hydrochloric acid in dichloroethane led to the desired β-ketonitrile **26** (Scheme 5).

In conclusion, it has been shown that a two-step Mizoroki–Heck coupling and hydrolysis procedure utilizing ethyl 3-ethoxyacrylate **1** and a readily available, conveniently handled catalyst with aryl or pyridyl halides provides ready access to novel substituted β-ketoesters in either library or batch platforms. Also, a similar method has been utilized in the formation of a β-ketonitrile. These simple processes offer a mild and generally applicable alternative for the synthesis of the structural diverse β-ketoesters and nitriles which may be employed in the subsequent construction of novel, substituted heterocycles.

Supplementary data

Supplementary data (for the NMR and mass spectra for the β-ketoesters **16**, **23a–23n**, and **26**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.10.076.

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17. *Typical procedure—preparation of* ***22c****:* A flask containing LiCl (980 mg, 23.1 mmol), 2-bromo-4-fluoroanisole (1.0 mL, 7.7 mmol), DCMA (1.8 mL, 8.4 mmol) and ethyl 3-ethoxyacrylate (3.3 mL, 23 mmol) in 1,4-dioxane (20 mL) was degassed by passing a stream of nitrogen through the mixture for 10 min. Bis(tri-*t*-butylphosphine) palladium(0) (166 mg, 0.32 mmol) was added, and reaction mixture was heated at reflux under nitrogen for 16 h. The brown mixture was then cooled and partitioned between ethyl acetate and water. The layers were separated, and the organic layer was washed sequentially with aqueous NH_4Cl and brine, followed by drying over Na_2SO_4. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give an oil which was purified by flash chromatography on silica (40 g, 10–50% ethyl acetate in heptane) to afford **22c** as an orange oil (1.93 g, 92%) as an inseparable mixture of *E*- and *Z*-isomers: ^{1}H NMR ($CDCl_3$, 500 MHz) alkene protons δ: 5.21, 5.33 ppm (1:1 ratio); LCMS (ES−): 269.2 (M−H). HRMS Calcd for $C_{14}H_{17}FO$: 269.1184. Found: 269.1196.
18. *Typical procedure—preparation of* ***23c****:* To a solution of **22c** (1.93 g, 7.18 mmol) in DCE (20 mL) was added 6 M HCl (6.0 mL, 40 mmol), and the biphasic mixture was stirred vigorously for 15 h at rt. The layers were then separated, and the DCE layer dried over Na_2SO_4. The mixture was filtered, and the filtrate concentrated to afford an orange oil which by NMR contains highly pure **22c** (1.58 g, 92%) as a 9:1 mixture of ketone and enol: Ketone ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.23 (t, 3H, J = 7.1 Hz), 3.88 (s, 3H), 3.96 (s, 2H), 4.18 (q, 2H, J = 7.1 Hz), 6.93 (dd, 1H, J = 9.15, 4.0 Hz), 7.16–7.24 (m, 1H), 7.59 (dd, 1H, J = 9.03, 3.17 Hz). Enol key peaks—6.10 (s, 1H, =CH), 12,69 (s, 1H, OH); LCMS (ES+); 241.2 (M+H). HRMS Calcd for $C_{12}H_{13}FO$: 241.0871. Found: 241.0873. In cases where substantial impurities were present in the hydrolysis step, the products were purified by silica flash chromatography with ethyl acetate and heptane to give product **23** as inseparable mixtures of the ketone and enol ranging from 9:1 to 1:1, respectively. When the reactions contained pyridyl derivatives, the aqueous layer containing the protonated product was made basic with saturated aqueous $NaHCO_3$ followed by extraction with ethyl acetate or dichloromethane to isolate the products.