Tetrahedron Letters 58 (2017) 898–901

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

One pot synthesis of unsymmetrical ketones from carboxylic and boronic acids via PyClU-mediated acylative Suzuki coupling

Pedro M. Garcia-Barrantes, Kevin McGowan, Steven W. Ingram, Craig W. Lindsley *

Departments of Chemistry and Pharmacology, Vanderbilt University, Nashville, TN 37232, United States

ARTICLE INFO

Article history:
Received 14 December 2016
Revised 19 January 2017
Accepted 20 January 2017
Available online 22 January 2017

Keywords:
PyClU
Suzuki-Miyaura
One pot
Cross-coupling
Boronic acid

ABSTRACT

A synthetic procedure for the preparation of ketones from easily accessible carboxylic acids has been developed. This methodology proceeds via *in situ* activation of the carboxylic acid with PyClU, followed by the palladium-catalyzed acylative cross-coupling with boronic acids. The reaction is performed in one pot, without the need of phosphine ligands, at room temperature and in reaction times of 2 h or less. The scope of the reaction is robust with aryl boronic and carboxylic acids.

The ketone functional group is a common moiety found in multiple substances with applications in diverse fields, such as pharmaceutical, agrochemical and materials. Ketone-containing compounds, and especially unsymmetrical aryl and/or heterobiaryl ketones, are important intermediates in organic synthesis that have been elaborated into both simple small molecule compounds as well as highly complex natural products and polymers. Due to their versatility and wide applicability, numerous methods and strategies for their preparation have been published.[1] However, many of these approaches have caveats, especially when it comes to the synthesis of unsymmetrical ketones, as they occur in either a multi-step fashion, under harsh conditions, or with low tolerance for pendant functional groups.

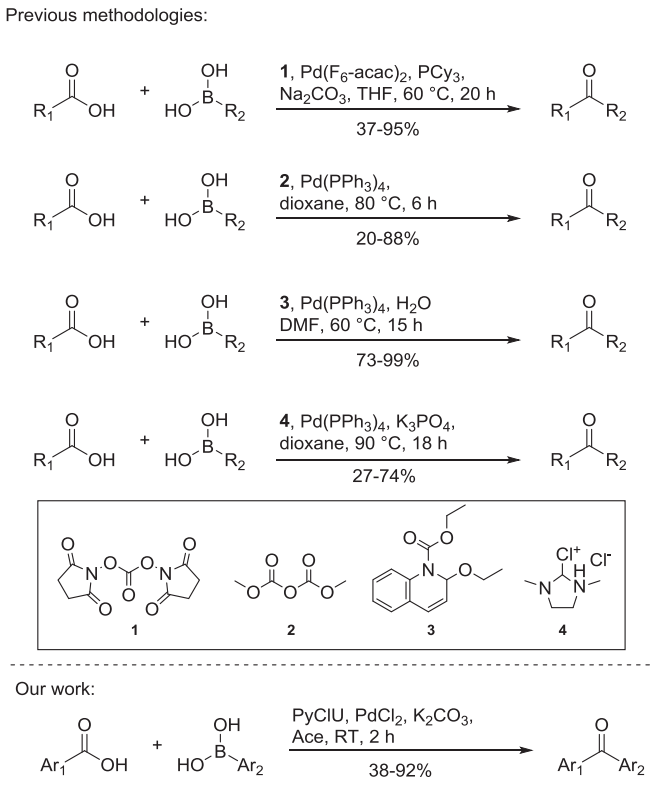
The preparation of aryl ketones has been facilitated significantly with the introduction of Suzuki cross-coupling reactions between acyl chlorides and organoboranes.[2–4] This approach has the advantage of being operationally simple, without the necessity of ligands for the metal, and often at room temperature; however, the use of acyl chlorides has its disadvantages: they usually need to be prepared in a prior step, chemical instability in open atmosphere, and they are not as ubiquitous in commercial catalogs as other carboxylic acid derivatives. In order to bypass the use of acyl halides and expand the applicability of this reaction, various approaches have been developed where the carboxylic acid is pre-activated to form a suitable species that can enter in the catalytic cycle of this transformation.

Representative of these latter pre-activation strategies, the use of di(*N*-succinimidyl) carbonate **1**,[5] dimethyl dicarbonate **2**,[6–8] *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline **3**,[9] and 2-chloro-1,3-dimethylimidazolidinium chloride **4** have been reported (Scheme 1).[10] These reagents allow the conversion of carboxylic acids to mixed anhydrides, activated esters, or acyl chlorides, species which can take part of the reaction with boronic acids in a Suzuki coupling. However, long reaction times and thermal heating (60–90 °C) are required for the reaction to occur when using these methodologies, as well as phosphine ligands, that can complicate purification. More recently, the use of **1** to form unsymmetrical ketones at room temperature has been highlighted; however, this transformation still required reaction times between 12 and 24 h and employs high-order aryl boron reagents, which are far less available than boronic acids.[11]

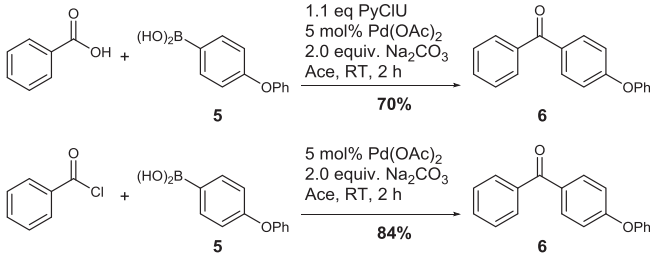
In the course of our drug discovery efforts, an early lead series required the synthesis of unsymmetrical ketone intermediates; therefore, we took the opportunity to develop new methodology for the *in situ* activation of carboxylic acids in acylative Suzuki couplings with boronic acids. Based on the broad substrate scope in amide coupling paradigms, we focused on PyClU, which can efficiently generate the acyl chloride species *in situ*. Also, the urea by-product derived from the PyClU is not likely to interfere in the reaction. In an initial pilot of this approach, we assessed the coupling using benzoic acid and **5** as model system, which provided **6** in good yield (70%, Scheme 1). Direct comparison of this

* Corresponding author.
E-mail address: craig.lindsley@vanderbilt.edu (C.W. Lindsley).

http://dx.doi.org/10.1016/j.tetlet.2017.01.064
0040-4039/



Scheme 1. Formation of ketones via cross-coupling of carboxylic and boronic acids.



Scheme 2. Comparison of the Suzuki coupling conditions employing benzoyl chloride and via PyClU-activated benzoic acid.

Table 1
Screening of bases for PyClU-mediated acylative Suzuki coupling.[a]

Entry	Base	Equiv.	Yield[b]
1	No base	–	0
2	K_2CO_3	2.0	79
3	Na_2CO_3	2.0	59 (70)
4	Cs_2CO_3	2.0	47
5	K_3PO_4	2.0	57
6	CsF	2.0	23
7	KOH	2.0	2
8	NaOH	2.0	23
9	*t*-BuOK	2.0	0
10	Et_3N	2.0	36
11	DIEA	2.0	22
12	2,4,6-Collidine	2.0	0
13	K_2CO_3	1.0	83
14	K_2CO_3	3.0	78
15	Na_2CO_3	1.0	79
16	Na_2CO_3	3.0	55
17	K_3PO_4	1.0	59
18	K_3PO_4	3.0	50

[a] Reactions were run in a 0.5 mmol scale, using benzoic acid (1.0 equiv.), 4-phenosyphenylboronic acid (1.0 equiv.), PyClU (1.1 equiv.), 5 mol% $Pd(OAc)_2$ in acetone (0.2 M), 2 h of reaction time at room temperature.
[b] Yields were determined by LC-MS, using as IS 3-phenoxybenzoic acid.

Table 2
Screening of palladium sources for optimization of the PyClU-mediated acylative Suzuki coupling.[a]

Entry	Catalyst	Mol%	Yield[b]
1	No palladium	–	0
2	Pd/C	5	15
3	$PdCl_2$	5	89
4	$Pd(acac)_2$	5	7
5	$Pd_2(dba)_3$	5	14
6	$Pd(PPh_3)_4$	5	0
7	$Pd(PPh_3)_2Cl_2$	5	9
8	$Pd(P(t\text{-}Bu)_3)_2$	5	41
9	$Pd(dppf)Cl_2$	5	15
10	$Pd(OAc)_2$	2	49[c]
11	$Pd(OAc)_2$	1	43[c]
12	$PdCl_2$	2	74[c]
13	$PdCl_2$	1	60[c]

[a] Reactions were run as indicated in Table 1, using K_2CO_3 (1.0 equiv.) as base.
[b] Yields were determined by LC-MS, using 3-phenoxybenzoic acid as IS.
[c] 4 h of reaction time.

new this methodology to the classical approach with benzoyl chloride, demonstrated that the two approaches were comparable (84%, Scheme 2).

As initial results demonstrated that using PyClU was a viable strategy to perform the reaction with the carboxylic acid *in situ*, we proceeded to screen conditions to optimize the yield of the transformation. The first step of our screening included the use of different bases (Table 1). This effort demonstrated that the use of base was essential, as without this reaction component, no product was observed. Also, it was found that carbonate and phosphate bases (entries 2–5 and entries 13–18, Table 1) were superior to organic bases (entries 10–12, Table 1) and alkoxides (entries 7–9, Table 1). The equivalents of base also affected the outcome of the reaction, with one equivalent affording comparable or improved results relative to three equivalents of base. Thus, the first optimization parameter identified that one equivalent of potassium carbonate provided the best results (83% yield, entry 13, Table 1), and these conditions would be employed in subsequent optimization parameters.

Then, we explored different catalysts previously used in Su-zuki cross-couplings (Table 2). The use of copper (Cu_2O, CuOAc, CuCl, CuBr and CuI) and nickel ($NiCl_2$, $Ni(acac)_2$, $Ni(COD)_2$ and $Ni(PPh_3)_2Cl_2$) sources failed to deliver the desired product **6**. In contrast, palladium catalysts gave mixed results; however, $PdCl_2$ stood out (entry 3, Table 2), providing improved conversion relative to Pd $(OAc)_2$. Importantly, these data demonstrated that additional phosphine ligands are not necessary for a successful reaction. Attempts to decrease the catalyst loading from 5 mol% to either 1 or 2 mol% resulted in diminished yields and slower conversion to product (entries 10–13, Table 2). Overall, these data support the use of 5 mol% $PdCl_2$ as the optimal catalyst in the PyClU-mediated acylative Suzuki coupling.

With the optimal base (K_2CO_3) and catalyst (5 mol% $PdCl_2$) identified, we next explored the effect of solvents on the reaction (Table 3). Interestingly, we observed that the reaction could be performed in in moderate yields both non-polar and polar aprotic solvents obtaining moderate yields, while protic solvents negatively impacted yields and further diminished as the dielectric constant increased. Competent solvents from this effort were toluene (entry 2, Table 3) and THF (entry 4, Table 3); however, despite achieving yields in excess of 60%, neither produced an improvement over acetone (entry 1, Table 3).

Table 3
Screening of solvents for optimization of the PyClU-mediated acylative Suzuki coupling.[a]

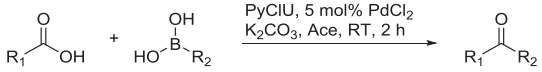
Entry	Solvents	Yield[b]
1	Acetone	89
2	Toluene	62
3	1,4-Dioxane	47
4	THF	68
5	DME	49
6	EtOAc	57
7	DMF	0
8	ACN	39
9	*i*-PrOH	40
10	EtOH	40
11	MeOH	25
12	H_2O	0

[a] Reactions were performed as in Table 1, using K_2CO_3 (1.0 equiv.), 5 mol% $PdCl_2$ in the respective solvent (0.2 M).
[b] Yields were determined by LC-MS, using as IS 3-phenoxybenzoic acid.

Then, we proceeded to test the scope of the PyClU-mediated acylative Suzuki coupling with the optimized conditions generated.[12] Initially, we explored a broad range of substituents in both the carboxylic acid and the boronic acid reaction components. Quickly, we found that sp^3 coupling partners, either carboxylic acid or boronic acid, did not afford the desired ketones; thus, reaction scope was limited to aromatic and heteroaromatic coupling partners (Table 4). To explore electronic effects on the aryl/heteroaryl carboxylic acid coupling partner in this reaction, we selected both electron donating groups (methyl) and electron withdrawing groups (chlorine). The different toluic acid (**8**–**10**, Table 4) showed little difference in their yields, indicating that electron-donating substituents generally allowed. In the case of the electron-withdrawing chlorine atom, the 2-chloro substitution (**11**) led to lower yields (56%), compared the 3- and 4-substituted congeners, **12** (85%) and **13** (74%), respectively. Our survey of reaction scope was expanded to include a broader array of electron-donating and withdrawing substituents, predominantly 4-position of the benzoic acid component. The optimized conditions tolerated the presence of electron withdrawing substituents such as fluoro (**14**,**15**), trifluoromethyl (**18**), trifluoromethoxy (**19**), cyano (**16**,**17**) and nitro (**20**). From this effort, it was observed that the nitro and cyano led to lower yields while other substituents afforded isolated yield between 61 and 76%. Electron-donating substituents such as methoxy (**21**) also provided good isolated yields, as well as the use of the Boc-protected aniline (**22**). Based on these data, we expanded the scope further to survey heterocyclic ring systems; however, limited tolerance to heteroatoms in the ring was noted. The best results were obtained, with furan (**23**), thiophene (**24**) and MeO-pyridine (**25**). Basic heterocycles such as naked pyridine, imidazole, as well as NH-containing rings systems, such as pyrazole and indole, failed to deliver the desired product.

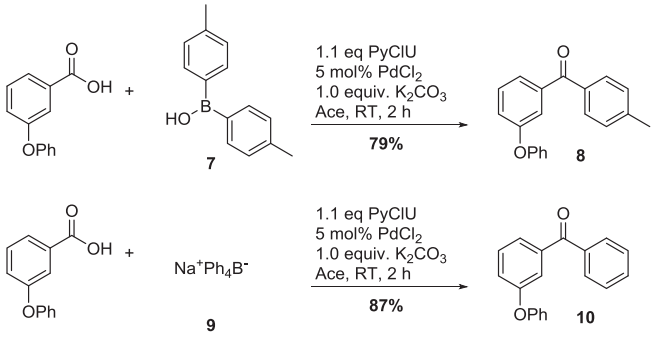
To explore the effect of electron donating or electron withdrawing substituents on the boronic acid (Table 4) in this reaction, the methoxy (**26**–**28**) and cyano (**29**,**30**) moieties were initially evaluated. The different anisole boronic acids showed similar yields though the 2-methoxy (**26**) had a low conversion rate at the two hour time point. The electron-withdrawing cyano

Table 4
Scope of PyClU-mediated acylative Suzuki coupling.



Cpd	R^1	R^2	Conversion[b]	Yield[c]
7	Ph	4-PhOPh	91	89
8	2-MePh	4-PhOPh	>98	92
9	3-MePh	4-PhOPh	>98	77
10	4-MePh	4-PhOPh	>98	86
11	2-ClPh	4-PhOPh	68	56
12	3-ClPh	4-PhOPh	>98	85
13	4-ClPh	4-PhOPh	>98	74
14	3-FPh	4-PhOPh	>98	63
15	4-FPh	4-PhOPh	>98	76
16	3-CNPh	4-PhOPh	85	80
17	4-CNPh	4-PhOPh	62	38
18	4-CF_3Ph	4-PhOPh	79	61
19	4-CF_3OPh	4-PhOPh	81	70
20	4-NO_2Ph	4-PhOPh	71	50
21	3-MeOPh	4-PhOPh	>98	78
22	4-NHBocPh	4-PhOPh	>98	79
23	2-Furan	4-PhOPh	77	50
24	5-Me-2-Thiophene	4-PhOPh	79	69
25	6-MeO-3-Pyridine	4-PhOPh	71	68
26	Ph	2-MeOPh	54	29
27	Ph	3-MeOPh	86	51
28	Ph	4-MeOPh	82	54
29	Ph	3-CNPh	95	60
30	Ph	4-CNPh	77	44
31	3-PhOPh	4-MePh	86	67
32	3-PhOPh	4-FPh	92	45
33	3-PhOPh	4-ClPh	86	59
34	3-PhOPh	4-CF_3Ph	90	79
35	3-PhOPh	4-CF_3OPh	82	49
36	3-PhOPh	3-Thiophene	80	60

[a] Reactions were run as in Table 1, using K_2CO_3 (1.0 equiv.), 5 mol% $PdCl_2$.
[b] Conversion with respect to the boronic acid.
[c] Isolated yields.



Scheme 3. Production of unsymmetrical ketones with higher-order boron reagents and PyClU mediated conditions.

substituent provided comparable yields in either the 3- (**29**) or 4-position (**30**), but the 2-CN congener afforded no product. We further expanded our scope by introducing a range of electron-donating and electron-withdrawing groups at the 4-position (**31**–**35**), which were all tolerated under our optimized conditions. We then tried to broaden our scope to heterocyclic boronic acids, but only the thiophene derivative (36) proved productive.

Lastly, we wanted to assay higher-order boron reagent partners, as Zou and collaborators demonstrated that the acylative Suzuki coupling could be performed also with aryl borinic acids and tetraarylboronates.[11] Performing the reaction with p-tolylborinic acid **7** under our optimized conditions provided ketone **8** in yields comparable to those reported Zou.[11] Furthermore, the use of tetraphenylboronate **9** also delivered ketone **10** in good yields (87%), suggesting broad generality amongst boron species (Scheme 3).

In summary, we have developed a novel approach for the acylative Suzuki coupling between readily available and stable carboxylic and boronic acids, as well as higher order boron reagents (e.g. borinic acids).[11] By using PyClU as the *in situ* activating reagent of the carboxylic acid, we accomplish the transformation to unsymmetrical ketones at room temperature, without the need of phosphine ligands, and in short reaction times (up to 2 h). The methodology has proved to be robust to synthesize different unsymmetrical aryl ketones in moderate to high yields, and with tolerance for electron-withdrawing and electron-releasing substituents.

Acknowledgments

The authors gratefully acknowledge support from the Warren Family and Foundation for support of our research programs and for establishing the William K. Warren, Jr. Chair in Medicine.

References

1. Dieter RK. *Tetrahedron*. 1999;55:4177–4236.
2. Bykov VV, Korolev DN, Bumagin NA. *Russ Chem Bull*. 1997;46:1631–1632.
3. Bumagin NA, Korolev DN. *Tetrahedron Lett*. 1999;40:3057–3060.
4. Haddach M, McCarthy JR. *Tetrahedron Lett*. 1999;40:3109–3112.
5. Gooßen L, Ghosh K. *Chem Commun*. 2001;2084–2085.
6. Kakino R, Narahashi H, Shimizu I, Yamamoto A. *Chem Lett*. 2001;1242–1243.
7. Gooßen LJ, Winkel L, Döhring A, Ghosh K, Paetzold J. *Synlett*. 2002;1237–1240.
8. Kakino R, Narahashi H, Shimizu I, Yamamoto A. *Bull Chem Soc Jpn*. 2002;75:1333–1345.
9. Kwon Y-B, Choi B-R, Lee S-H, Seo J-S, Yoon C-M. *Bull Korean Chem Soc*. 2010;31:2672–2674.
10. Pathak A, Rajput CS, Bora PS, Sharma S. *Tetrahedron Lett*. 2013;54:2149–2150.
11. Si S, Wang C, Zhang N, Zou G. *J Org Chem*. 2016;81:4364–4370.
12. General experimental procedure. In a vial, 4-phenoxyphenylboronic acid (87 mg, 0.410 mmol), $PdCl_2$ (3.7 mg, 0.020 mmol), 1-(chloro-1-pyrrolidinylmethylene)pyrrolidinium hexafluorophosphate (PyClU) (150 mg, 0.450 mmol), K_2CO_3 (57.41 mg, 0.410 mmol) were added and dissolved in 1 ml of acetone. Then, a solution of benzoic acid (50 mg, 0.410 mmol) in 1 ml of acetone was added. The mixture was stirred at room temperature for 2 h. Consumption of starting materials and formation of product was confirmed by LC-MS. The reaction was worked up filtration through a small pad of celite and evaporating the volatiles *in vacuo*. The crude product was obtained as a white solid (100 mg, 89% yield) after flash chromatography purification using a gradient hexanes and ether, 0 to 5% ether. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.85 (2H, d, *J* = 8.6 Hz), 7.81 (2H, d, *J* = 8.4 Hz), 7.60 (1H, t, *J* = 7.36 Hz), 7.50 (2H, t, *J* = 7.3 Hz), 7.43 (2H, t, *J* = 7.7 Hz), 7.23 (1H, t, *J* = 7.4 Hz), 7.13 (2H, d, *J* = 7.7 Hz), 7.06 (2H, d, *J* = 8.8 Hz). LRMS: m/z = 275 [MH^+]