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A Concise Access to 3-Substituted 2-Pyrones.

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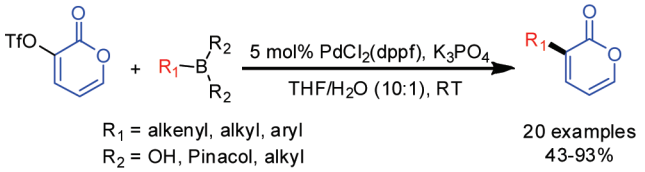


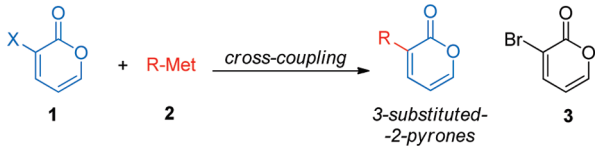
The development of a modular synthesis of 3-substituted-2-pyrones is described. The attainment of this strategy hinges on a new electrophilic pyrone derivative which can be readily prepared on a multigram scale and which performs very competently in metal-catalyzed cross-coupling reactions with a variety of nucleophiles.

2-Pyrones are an important class of organic compounds forming the backbone of many naturally occurring, biologically active substances.[1] The synthesis of substituted 2-pyrones through cross-coupling chemistry has been extensively studied, and 5-bromo- and 3,5-dibromo-2-pyrones were by far the most often-studied electrophiles thus far. These derivatives have been employed in metal-catalyzed coupling reactions with nucleophilic arylstannanes, alkynes, and arylboronic acids or themselves converted to the corresponding tin, boron, zinc, and copper derivatives for cross-coupling with electrophiles.[1d,2]

Within the context of a research program aimed at exploiting the photochemistry of 2-pyrones,[3] we required an expeditious access to various 3-substituted (alkyl, alkenyl, aryl) 2-pyrones. Much to our surprise, the synthesis of such simple derivatives, lacking any additional activating functional groups,[2g,h,4] is poorly precedented and frequently cumbersome. For example, the literature synthesis of perhaps the simplest derivative, 3-methyl-2-pyrone, requires five chemical steps from commercially available δ-valerolactone (involving an enolate alkylation with methyl iodide).[4] Furthermore, the extension of this synthesis to other 3-alkyl-2-pyrones is not feasible: the enolate of δ-valerolactone failed to produce alkylated products with more complex electrophiles in synthetically useful yields.[5]

We therefore became interested in developing a rapid and modular access to 3-substituted 2-pyrones. In particular, it appeared logical to employ a "universal" electrophilic 2-pyrone reagent **1** that could be cross-coupled to a variety of readily available organometallic nucleophiles **2** under transition metal catalysis (Scheme 1). Literature precedent, however, was not favorable to our prospects: what would have been a logical candidate, 3-bromo-2-pyrone (**3**), was reportedly unresponsive to palladium catalysis, which eventually stimulated the previous development of 3-stannyl-2-pyrone derivatives for use as nucleophiles.[2a]

SCHEME 1. Proposed Modular Blueprint to Access 3-Substituted 2-Pyrones



We nevertheless decided to begin our investigations with **3** and turned our attention to cross-coupling reactions with Grignard reagents. Iron catalysis in cross-coupling reactions has recently received much attention, after its revival at the end of last century.[6] In particular, iron(III) salts have been shown to display reactivity more commonly associated with *d*-block metals while retaining the environmental and toxicity benefits typical of alkali or alkaline earth metals.[7] In addition to the low cost and ready availability of the required iron salts, the high reaction rates and mild conditions employed make these cross-coupling reactions very appealing to the synthetic practitioner.[8]

(1) (a) McGlacken, G. P.; Fairlamb, I. J. S. *Nat. Prod. Rep.* **2005**, *22*, 369. (b) Schlingmann, G.; Milne, L.; Carter, G. T. *Tetrahedron* **1998**, *54*, 13013. (c) Barrero, A. F.; Oltra, J. E.; Herrador, M. M.; Sanchez, J. F.; Quilez, J. F.; Rojas, F. J.; Reyes, J. F. *Tetrahedron* **1993**, *49*, 141. (d) Fairlamb, I. J. S.; Marrison, L. R.; Dickinson, J. M.; Lu, F.-J.; Schmidt, J. P. *Bioorg. Med. Chem.* **2004**, *12*, 4285. (e) Wu, P.-L.; Hsu, Y.-L.; Wu, T.-S.; Bastow, K. F.; Lee, K.-H. *Org. Lett.* **2006**, *8*, 5207.

(2) (a) Liu, Z.; Meinwald, J. *J. Org. Chem.* **1996**, *61*, 6693. (b) Kim, W.-S.; Kim, H.-J.; Cho, C.-G. *J. Am. Chem. Soc.* **2003**, *125*, 14288. (c) Thanh Tam, N.; Cho, C.-G. *Org. Lett.* **2008**, *10*, 601. (d) Thanh Tam, N.; Chang, J.; Jung, E.-J.; Cho, C.-G. *J. Org. Chem.* **2008**, *73*, 6258. (e) Thanh Tam, N.; Jung, E.-J.; Cho, C.-G. *Org. Lett.* **2010**, *12*, 2012–2016. (f) Lee, J.-H.; Park, J.-S.; Cho, C.-G. *Org. Lett.* **2002**, *4*, 1171. (g) Kim, W.-S.; Kim, H.-J.; Cho, C.-G. *Tetrahedron Lett.* **2002**, *43*, 9015. (h) Lee, J.-H.; Kim, W.-S.; Lee, Y. Y.; Cho, C.-G. *Tetrahedron Lett.* **2002**, *43*, 5779. (i) Ryu, K.; Cho, Y.-S.; Jung, S.-I.; Cho, C.-G. *Org. Lett.* **2006**, *8*, 3343. (j) Posner, G. H.; Harrison, W.; Wettlaufer, D. G. *J. Org. Chem.* **1985**, *50*, 5041.

(3) Frébault, F.; Luparia, M.; Oliveira, M. T.; Maulide, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 5672; *Angew. Chem.* **2010**, *122*, 5807.

(4) Shi, X.; Leal, W. S.; Liu, Z.; Schrader, E.; Meinwald, J. *Tetrahedron Lett.* **1995**, *36*, 71.

(5) For a rare example, see: Khouri, F. F.; Khaloustian, M. K. *J. Am. Chem. Soc.* **1986**, *108*, 6683.

(6) (a) Sherry, B. D; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500. (b) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856. (c) Czaplik, W. M.; Mayer, M.; Cvengros, J.; Wangelin, A. J. *ChemSusChem* **2009**, *2*, 396. (d) Hatakeyama, T.; Hashimoto, T.; Kondo, Y.; Fujiwara, Y.; Seike, H.; Takaya, H.; Tamada, Y.; Ono, T.; Nakamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 10674.

(7) (a) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217. (b) Nakamura, E.; Yoshikai, N. *J. Org. Chem.* **2010**, *75*, 6061. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 1364.

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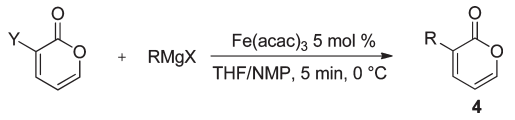
TABLE 1. Iron-Catalyzed Couplings of 3, 6, and 7 with Grignard Reagents



entry	Y	RMgX	products	yield[a] (%)
1	Br (**3**)	MeMgBr	**4a**	85
2	Br (**3**)	BuMgCl	**4b**	(60)
3	Br (**3**)	^{i}PrMgBr	**4c**	(33)
4	OTs (**6**)	MeMgBr	**4a**	30[b]
5	OTf (**7**)	MeMgBr	**4a**	44
6	OTf (**7**)	BuMgCl	**4b**	37
7	OTf (**7**)	PhMgCl	**4d**	(40)
8	OTf (**7**)	PhMgBr	**4d**	(63)
9	OTf (**7**)	CH_2=CHMgCl		0

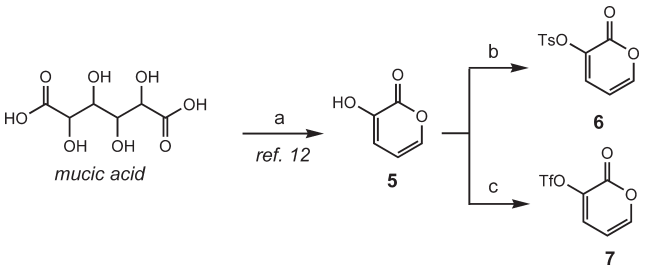
[a]Isolated yield of pure product. Conversions are listed in parentheses (as determined by ^{1}H NMR). [b]Reaction performed at −15 °C.

In the event (Table 1), and after extensive screening of reaction conditions, the coupling of **3** with methylmagnesium bromide could be induced to proceed in excellent isolated yield (on a 0.3 mmol scale).[9] Unfortunately, conversions dropped significantly as soon as higher homologues were employed, and the isolated yields consequently plummeted. It appears that **3** is indeed an electrophile with limited reactivity toward most cross-coupling protocols. At this juncture, we also acknowledged that the low-yielding standard three-step synthesis of **3** from the expensive 5,6-dihydro-2-pyrone[10] was detrimental to our aims of efficiency and sought the development of a different surrogate to the electrophilic synthon **1**. Inspired by precedent suggesting that tosylates and triflates would fare better as leaving groups,[6a,11] we targeted the preparation of 3-tosyloxy-2-pyrone (**6**) and 3-triflyloxy-2-pyrone (**7**) for use as coupling partners.

The common precursor for these two electrophiles was 3-hydroxy-2-pyrone (**5**) (Scheme 2), which was prepared as previously reported through large-scale pyrolysis of the cheap mucic acid.[12] Treatment of **5** with either tosyl chloride or triflic anhydride delivered the (to the best of our knowledge) hitherto unknown pyrones **6** and **7**.

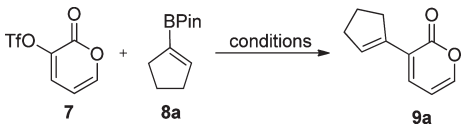
As depicted in Table 1, while **6** proved to be a weak coupling partner (entry 4), 3-triflyloxy-2-pyrone (**7**) was more promising (entries 5−8). Its higher reactivity was highlighted by the full conversions observed with methyl- and butylmagnesium halides. Unfortunately, significant decomposition induced by the Grignard reagent (confirmed through background experiments) lowered the isolated yields. In addition, less reactive aryl and alkenyl Grignard reagents still did not provide acceptable results.

SCHEME 2. Synthesis of 3-Tosyloxy- and 3-Triflyloxy-2-pyrone[a]



[a]Reagents and conditions: (a) KH_2PO_4, P_4O_{10}, neat, 150 °C, 40%; (b) TsCl, NEt_3, DMAP, r.t., 70%; (c) Tf_2O, 2,6-collidine, DCM, 0 °C, 85%.

TABLE 2. Optimization of the Suzuki Coupling between 7 and 8a[a]



entry	conditions[a]	yield[b] (%)
1	$Pd(OAc)_2$, P(*t*Bu) $_2$(bph), KF, THF, 50 °C, 24 h	42
2	$Pd(OAc)_2$, PPh_3, KF, dioxane/H_2O, rt, 3 h	49
3	$Pd(OAc)_2$, PPh_3, K_3PO_4, dioxane/H_2O, rt, 2 h	62
4	$Pd(OAc)_2$, PPh_3, Cs_2CO_3, dioxane/H_2O, rt, 3 h	57
5	$PdCl_2$(dppf), K_3PO_4, THF/H_2O, rt, 1 h	88
6[c]	$PdCl_2$(dppf), K_3PO_4, THF/H_2O, rt, 7 h	57

[a]In all reactions, 5 mol % of Pd catalyst and 10 mol % of ligand were used. [b]Isolated yield of pure product. [c]3-Bromo-2-pyrone (**3**) used as starting material.

Though disappointing, these initial setbacks provided us with new, previously untested pyrone electrophiles **6** and **7**. Their short and efficient syntheses additionally made them auspicious candidates for the fulfillment of the original strategy outlined in Scheme 1. We therefore decided to investigate the Suzuki coupling reaction[13] between **7** and organoboron reagents.

The catalytic merger of **7** and cyclopentenyl boronic acid pinacol ester **8a**[14] was investigated under diverse conditions, as summarized in Table 2. It was found early on that the presence of water in the mixture dramatically increased the reaction rate (entries 1 and 2), whereas changing the base did not have a marked impact (entries 2−4). $PdCl_2$(dppf) proved to be the catalyst of choice as it led to very fast coupling in an excellent yield of 88% (entry 5). As might be expected, employing 3-bromo-2-pyrone (**3**) as electrophilic partner (entry 6) resulted in a significantly lower reaction rate and poorer chemical yield. This rate difference between **7** and **3** is probably caused by the reported ability of triflate, as a leaving group, to accelerate the transmetalation process.[15]

Under the best conditions, we proceeded to investigate the scope of this transformation, beginning with alkenyl- and alkylboron derivatives (Table 3). Five- to seven-membered

(8) (a) Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3943. (b) Maulide, N.; Vanherck, J.-C.; Markó, I. E. *Eur. J. Org. Chem.* **2004**, 3962. (c) Nicolaou, K. C.; Chakraborty, T. K; Piscopio, A. D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.* **1993**, *115*, 4419. (d) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1992**, *114*, 2260. For further examples of application to total synthesis, see ref 6b and references cited therein.

(9) See the Supporting Information for details.

(10) Posner, G. H.; Afarinkia, K.; Dai, H. *Org. Synth.* **1998**, *9*, 112. For an alternative synthesis of **3** by decarboxylation, see: Cho, C.-G.; Park, J.-S.; Jung, I.-H.; Lee, H. *Tetrahedron Lett.* **2001**, *42*, 1065.

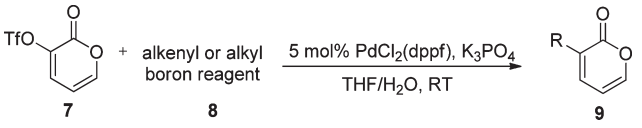
(11) Gøgsig, T. M.; Lindhardt, A. T.; Skrydstrup, T. *Org. Lett.* **2009**, *11*, 4886.

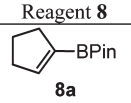
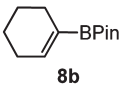
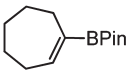
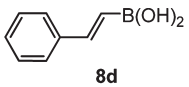
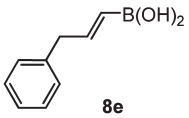
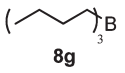
(12) Profitt, J. A.; Jones, T.; Watt, D. S. *Synth. Commun.* **1975**, *5*, 457.

(13) (a) Miyaura, N. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; Chapter 2. For reviews, see: (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (c) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.

(14) Prepared from cyclopentanone via Shapiro reaction of the corresponding hydrazone; see: Rauniyar, V.; Zhai, H.; Hall, D. G. *Synth. Commun.* **2008**, *38*, 3984.

TABLE 3. Suzuki Couplings of 7 Alkenyl- and Alkylboron Derivatives



Entry	Reagent **8**	Time (h)	Product	Yield[a]
1	 **8a**	1	**9a**	88
2	 **8b**	2	**9b**	77
3	 **8c**	2	**9c**	80
4	 **8d**	3	**9d**	47
5	 **8e**	2	**9e**	72
6	 **8f**	0.5[b,c]	**9f**	65
7	 **8g**	16[c]	**9g**	43

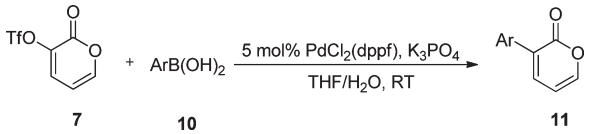
[a]Isolated yield of pure product. [b]Reaction carried out at 0 °C. [c]Commercially available 1 M solutions of **8f**−**g** in hexane were used.

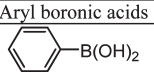
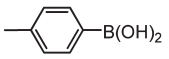
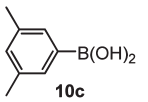
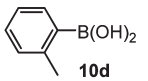
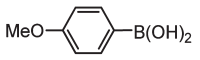
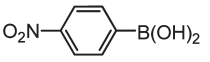
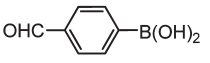
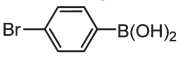
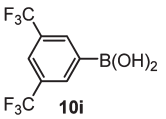
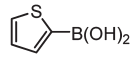
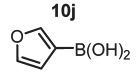
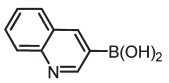
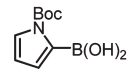
ring cycloalkenylboronic acid pinacol esters coupled readily with pyrone **7** (entries 1−3). (*E*)-Alkenylboronic acids afforded the cross-coupled products in moderate to good yields with complete retention of double bond geometry (entries 4 and 5). Under similar conditions, coupling of triethylborane was facile and yielded the desired 3-ethyl-2-pyrone (**9f**) in good yield. Reaction with tributylborane was slower but still delivered the coupled product **9g** in 43% yield.[16] The expeditious access to the previously unreported 3-alkyl-2-pyrones **9f** and **9g** presented herein stands in sharp contrast with the tedious route described for 3-methyl-2-pyrone,[4] a route which is furthermore not even applicable to higher homologues (such as **9f**,**g**).

We next examined Suzuki cross-coupling reactions of **7** with various arylboronic acids **10** (Table 4).

Once again, a broad variety of 3-aryl-2-pyrones could be obtained under the conditions optimized previously. Remarkably, both strong electron-withdrawing substituents (such as nitro- or trifluoromethyl, entries 6 and 9) and electron-donating moieties (entries 2, 3, and 5) led to facile coupling with **6** in less than 2 h at room temperature, giving the desired products in excellent yields. In addition, ortho-substituted boronic acids (entry 4) and heteroaryl derivatives

TABLE 4. Suzuki Couplings of 7 with Arylboronic Acids



Entry	Aryl boronic acids	Time (h)	Products	Yield[a]
1	 **10a**	1	**11a**	72
2	 **10b**	1	**11b**	87
3	 **10c**	1	**11c**	85
4	 **10d**	2	**11d**	72
5	 **10e**	0.5	**11e**	88
6	 **10f**	1	**11f**	74
7	 **10g**	1	**11g**	83
8	 **10h**	1	**11h**	83
9	 **10i**	1	**11i**	77
10	 **10j**	0.5	**11j**	53
11	 **10k**	1	**11k**	50
12	 **10l**	24	**11l**	51
13	 **10m**	0.5	**11m**	93

[a]Isolated yield of pure product.

(entries 10−13) were successful coupling partners. The reaction conditions tolerate the presence of a formyl functional group (entry 7) and no homocoupling product was observed with *p*-bromophenylboronic acid (entry 8).

In summary, we have developed a concise and efficient route toward 3-substituted 2-pyrones. Crucial to this end was the establishment of 3-triflyloxy-2-pyrone (**7**) as a readily available, highly reactive electrophilic synthon for metal-catalyzed cross-coupling reactions. Compound **7** underwent facile Suzuki reactions with a plethora of cycloalkenylboronic acid pinacol esters, alkenylboronic acids, trialkylboranes,

(15) (a) Stang, P. J.; Kowalski, M. H.; Schiavelli, M. D.; Longford, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 3347. (b) Stang, P. J.; Kowalski, M. H. *J. Am. Chem. Soc.* **1989**, *111*, 3356. (c) Hinkle, R. J.; Stang, P. J.; Kowalski, M. H. *J. Org. Chem.* **1990**, *55*, 5033. (d) Stang, P. J.; Cao, D. H.; Poulter, G. T.; Arif, A. M. *Organometallics* **1995**, *14*, 1110.

(16) Both triisopropyl- and tricyclohexylborane failed to give the desired products under these reaction conditions.

as well as aryl- and heteroarylboronic acids to give the corresponding 3-substituted 2-pyrones in good to excellent yields. As triflate **7** can be prepared in multigram scale in only two simple steps, the sequences presented herein effectively constitute scalable[17] and highly modular three-step syntheses of substituted pyrones.

Experimental Section

Representative Procedure for the Preparation of 3-Cyclopentenyl-2*H*-pyran-2-one (9a). A flask was charged with 3-(trifluoromethanesulfonyloxy)pyran-2-one (**7**) (37 mg, 0.15 mmol), $PdCl_2$(dppf) (6 mg, 5 mol %), K_3PO_4 (95 mg, 0.45 mmol, 3.0 equiv), and the boronic ester **8a** (35 mg, 0.18 mmol, 1.2 equiv). The flask was evacuated and backfilled with argon three times, and THF (0.7 mL) followed by water (0.07 mL) were added at rt. The mixture was stirred for 1 h and then diluted with EtOAc (10 mL). The organic layer was washed with saturated aqueous NH_4Cl solution (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash chromatography on a silica gel column using pentane/ethyl acetate (9:1) as eluant gave the title compound (21 mg, 88%) as a white solid: mp 54−55 °C; FTIR (neat) ν_{max} 3102, 2965, 2897, 2844, 1706, 1620, 1540; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (dd, J = 5.0, 1.9, 1H), 7.11 (dd, J = 6.7, 1.9, 1H), 7.04 (m, 1H), 6.25 (dd, J = 6.7, 5.0, 1H), 2.61−2.68 (m, 4H), 1.95 (q, J = 7.5, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9, 148.9, 136.0, 135.8, 135.2, 124.4, 106.6, 34.6, 33.6, 22.5; HRMS (ESI) calcd for $C_{10}H_{10}O_2$ $[M]^+$ 162.0683, found 162.0681.

(17) A 6 mmol scale reaction of **7** with **8a** gave the desired pyrone **9a** in 84% yield after the same period of time reported herein.

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Supporting Information Available: Experimental procedures, full characterization, and copies of NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.