Acyltrifluoroborate Reagents | Hot Paper

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A Reagent for the One-Step Preparation of Potassium Acyltrifluoroborates (KATs) from Aryl- and Heteroarylhalides**

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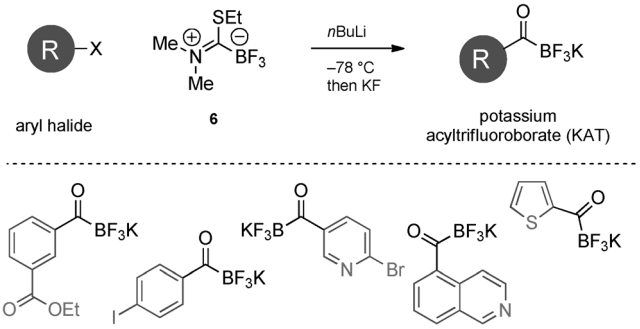
Dedicated to Professor Keisuke Suzuki on the occasion of his 60th birthday

Abstract: *Potassium acyltrifluoroborates (KATs) are fascinating functional groups whose further exploration is limited by poor synthetic access. Documented herein is the design and synthesis of a new reagent for their one-step preparation from aryl- and heteroarylhalides. The reagent is a stable, soluble zwitterion prepared by S-alkylation of a novel thioformamide trifluoroboronate. The KATs are prepared by adding one equivalent of nBuLi to a mixture of the aryl halide and the reagent at −78 °C. This protocol is suitable for the preparation of KATs containing pyridines, esters, nitro groups, and halides.*

Potassium acyltrifluoroborates (KATs) are fascinating functional groups that undergo rapid amide-forming ligations with hydroxylamines.[1] Although acylboron compounds have been long considered to be esoteric, unstable constructs,[2] we have found KATs to be easily handled solids that are stable to air and water. The further exploration of their chemistry and the use of their remarkably fast ligations[3] are currently hampered by poor synthetic access to these compounds. Molander et al. reported the first example in 2010 by lithiation of a methoxy vinyl ether, subsequent trapping with $B(OiPr)_3$, and treatment of the resulting vinylboron with KHF_2.[4] We documented a synthesis from benzotriazole acetals, suitable for preparing KATs, bearing simple aromatic and aliphatic side chains.[5] Unfortunately, the reaction conditions and workup (KHF_2) precluded the synthesis of many substrates, including those containing basic nitrogen atoms, esters, and even many aryl halides. KATs can be easily formed from acyl MIDA (MIDA = *N*-methyliminodiacetic acid) boronates,[6] which were recently prepared by Yudin and co-workers through a multistep synthesis.[7]

In this report we document a novel reagent for the one-step synthesis of KATs from aryl halides that is suitable for preparing a broad range of aromatic and heteroaromatic KATs (Scheme 1). Importantly, this method avoids the need for KHF_2 and is well suited for the preparation of heteroaryl KATs. It also introduces a new class of stable, soluble electrophilic trifluoroborate reagents which will be useful for other applications.



Scheme 1. One-step synthesis of acyltrifluoroborates.

At the outset of our studies, we sought to identify a reagent for the one-step conversion of organolithium reagents, which are commercially available or readily prepared under a variety of reaction conditions,[8] into acyltrifluoroborates. Furthermore, we hoped to incorporate the trifluoroborate moiety into the electrophilic reagent, with the aim of avoiding etching conditions[9] typically required for constructing it from boronic acids or esters. These considerations led us to the reagent designs shown in Scheme 2.

Potassium trifluorocyanoborate (**2**) is a known compound and readily prepared in one step from boron trifluoride diethyl etherate and potassium cyanide.[10] All attempts to add phenyl lithium to this reagent gave no identifiable products. We turned instead to formyl amide derivatives, which were previously unknown structures. Although lithiation of formamides is well known,[11] we were unable to trap the formamide anions with any electrophilic boron sources. In contrast, *N*,*N*-dimethyl thioformamide could be lithiated[12] and trapped with $B(OMe)_3$, which following treatment with KHF_2 gave the thioamide derivative **4**. Treatment of this compound with a mixture of KHF_2 and $NaNO_2$[13] afforded the formamide derivative **3**.

Unfortunately, the reagents **3** and **4** also proved unsuitable as electrophilic traps[14] for aryl lithiums. No addition products could be observed, an outcome we attributed largely to the poor solubility of the reagents at low temperature. Reasoning that formation of an internal zwitterionic salt would improve

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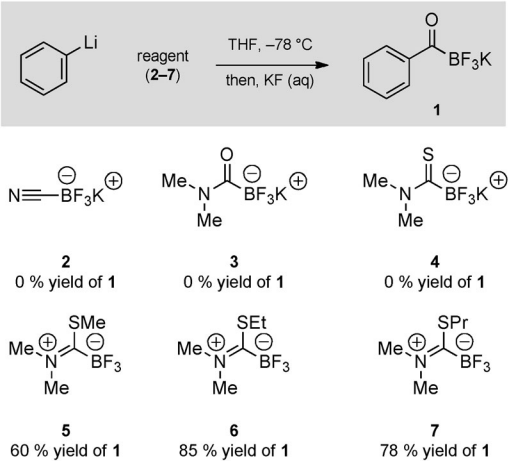
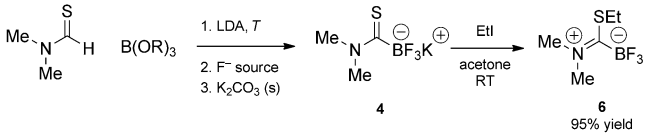


Scheme 2. Candidate reagents for introduction of acyltrifluoroborates. THF = tetrahydrofuran.

the solubility, we prepared reagents **5**–**7** by alkylation of **4** with the corresponding alkyliodides. The S-alkylations proceeded smoothly to give the imidates as stable compounds which were highly soluble in typical organic solvents.[15] We were pleased to find that phenyl lithium added smoothly to all three reagents, and after a suitable workup gave the corresponding KAT in good yield.

We selected the crystalline S-ethyl derivative **6** for further development. The *S*-propyl compound was an oil and the *S*-methyl compound was less soluble. Although the alkylation of **4** with EtI to give **6** proceeded smoothly, the preparation of **4** was plagued by low yields and poor reproducibility, particularly on larger scale. An extensive optimization study of the lithiation and trapping of *N*,*N*-dimethylthioformamide is summarized in Table 1. As noted by Seebach and co-workers,[12] maintaining the internal temperature of the lithiation below −100 °C proved to be critical for the success of the reaction. Furthermore, breakdown of the resulting tetrahedral intermediate was also an important parameter, which we

Table 1: Optimized synthesis of the reagent **6**.[a]



Entry	$B(OR)_3$	F^- source	T [°C][b]	Yield [%][c] **4**
1	$B(OMe)_3$	KHF_2 (aq)	−110	15
2	$B(OMe)_3$	HF (aq)	−110	40
3	$B(OEt)_3$	HF (aq)	−110	80
4	PinB(*i*OPr)	HF (aq)	−110	90[d]
5	$B(OEt)_3$	HF (aq)	−78	3

[a] All reactions were performed on a 16.8 mmol scale in THF (0.34 M). LDA was prepared at −78 °C with subsequent addition of $B(OR)_3$ and by *N*,*N*-dimethyl thioformamide at the indicated temperature. After 85 min, 9 equiv KHF_2 (aq) or 6 equiv HF (aq) were added as fluoride sources at −78 °C. [b] The dry ice/acetone bath was cooled to −110 °C with liquid N_2. [c] Yield of isolated product. [d] The product was contaminated with pinacol. LDA = lithium diisopropylamide.

eventually found was best achieved with aqueous HF[16] rather than KHF_2. The use of $B(OEt)_3$ in place of $B(OMe)_3$ gave a more stable intermediate and resulted in higher overall yields. These improvements made possible the preparation of **4** on a greater than 10 gram scale. Furthermore, the unpurified thioamide could be telescoped into the alkylation reaction to prepare **6** without isolation of the intermediate and without purification other than washing and filtration. The structure of **4** and its *S*-methyl derivative **5** were established by X-ray crystallography (Figure 1).

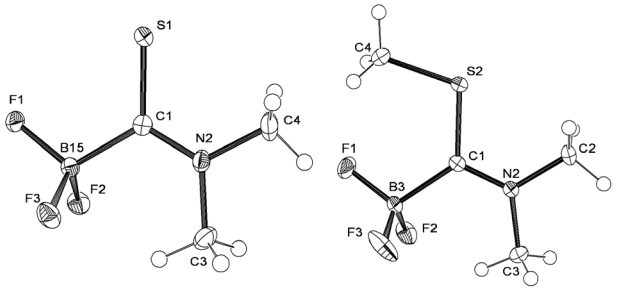


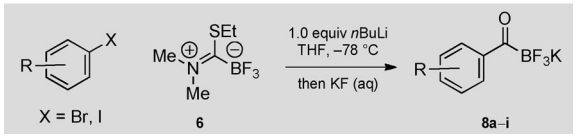
Figure 1. ORTEP drawings of **4** (left; counterion is not shown) and **5** (right). Thermal ellipsoids shown at 50% probability. CCDC 993821 and 993816 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

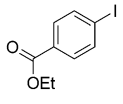
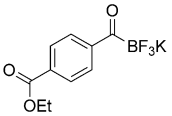
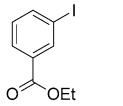
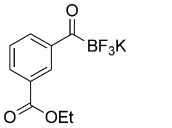
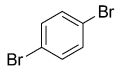
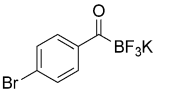
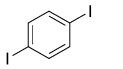
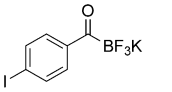
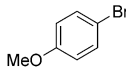
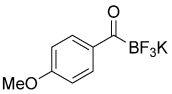
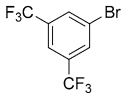
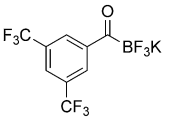
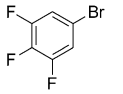
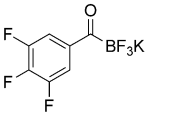
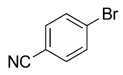
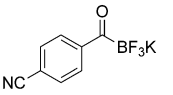
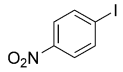
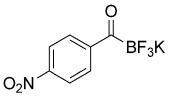
With a scalable synthesis of **6** established, we prepared aromatic KATs from the corresponding aryl halides (Table 2). After exploring several different protocols we found that lithium–halogen exchange with *n*BuLi at −78 °C in the presence of **6** proved to be the most general and highest yielding procedure. The in situ generated aryl lithium adds to **6** to give a tetrahedral intermediate, which can be observed by ^{1}H NMR analysis of the reaction. Decomposition of this intermediate to the KAT was best accomplished by the addition of aqueous KF to the reaction mixture at −78 °C. Like all organotrifluoroborates,[18] the ionic nature of KATs necessitates a good workup procedure. In our case, this was easily accomplished by addition of CH_2Cl_2 to precipitate the KAT, which was filtered and dissolved in acetone for isolation in good yield and purity. This protocol tolerated aryl halides, esters, nitro groups, and nitriles in the substrates.

The in situ generation and trapping of the aryl lithium could be smoothly extended to the synthesis of heteroaromatic KATs (Table 3), allowing the preparation of pyridine-derived KATs and their substituted variants. In a few cases, a small amount of **3**, formed by the decomposition of unreacted **6** during the reaction workup, is observed as a side product and can be difficult to completely remove from the desired product. This side product, however, does not participate in ligations with hydroxylamines.

In summary, we have developed a novel reagent suitable for the synthesis of potassium acyltrifluoroborates (KATs) from aryl- and heteroarylhalides. This protocol considerably expands the range of acyl boron compounds that can be prepared, opening an avenue for the further exploration and utilization of their unique chemistry. This work also introdu-

Table 2: Synthesis of aryl KATs with **6**.[a]

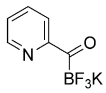
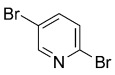
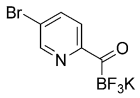
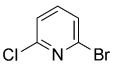
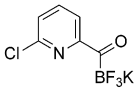
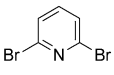
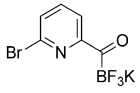
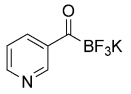
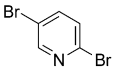
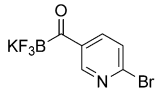
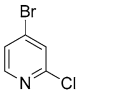
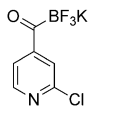
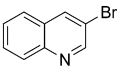
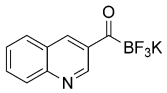
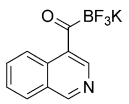
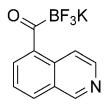


Entry	Substrate	Product		Yield [%][b]
1			**8a**	74
2			**8b**	79
3			**8c**	71
4			**8d**	48
5			**8e**	59
6			**8f**	89
7			**8g**	86
8			**8h**	86
9			**8i**	44

[a] All reactions were performed on a 1.08 mmol scale in THF (0.54 M) by addition of *n*BuLi to a mixture of the arylhalide and **6**. [b] Yield of isolated product.

ces several new classes of boronates, including thioformamide, formamide, and imidate derivatives. These stable, easily handled compounds are likely to possess unexplored chemical and physical properties.

Table 3: Synthesis of heteroaromatic KATs with **6**.[a]

Entry	Substrate	Product		Yield [%][b]
1			**9a**	60[c]
2			**9b**	70[c,d]
3			**9c**	81
4			**9d**	66
5			**9e**	69
6			**9f**	95
7			**9g**	90
8			**9h**	77
9			**9i**	35
10			**9j**	30
11			**9k**	89
12			**9l**	65
13			**9m**	64

[a] All reactions were performed on a 1.08 mmol scale in THF (0.54 M). [b] Yield of isolated product. [c] This KAT was insoluble in acetone and the yield was determined by NMR spectroscopy. Further isolation steps were required. [d] Toluene was used as the solvent.[17]

Experimental Section

In a flame-dried, 10 mL round-bottom flask under an atmosphere of dry N_2, reagent **6** (0.200 g, 1.08 mmol, 1.00 equiv) and an arylhalide (1.08 mmol, 1.00 equiv) were dissolved in THF (2 mL) and cooled to −78 °C in a dry ice/acetone bath. *n*-Butyllithium (1.6 M in hexane, 675 μL, 1.08 mmol, 1.00 equiv) was added dropwise over 30 min by syringe pump. One hour after the end of *n*-butyllithium addition, acetone (80 μL, 1.08 mmol, 1.00 equiv) was added to quench the residual *n*-butyllithium, and 10 min later 0.5 mL aqueous KF solution (6.5 M, 3.24 mmol, 3.00 equiv) was added. The flask was removed from the bath and stirred for one hour. CH_2Cl_2 (2 mL) was added to this heterogeneous mixture and the solution was stirred and filtered. The solids were washed three times with CH_2Cl_2 (the THF and CH_2Cl_2 filtrate contained the residual aryl halide and reagent **6**). The remaining filter cake (product and inorganic salts) was washed multiple times with acetone (2–50 mL) until the resulting filtrate was colorless (note: the solution containing product is yellow). Acetone was removed under reduced pressure and the product (**8** or **9**) was obtained as a white or yellow solid.

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[1] A. M. Dumas, G. A. Molander, J. W. Bode, *Angew. Chem. Int. Ed.* **2012**, *51*, 5683 – 5686; *Angew. Chem.* **2012**, *124*, 5781 – 5784.

[2] a) M. Yamashita, Y. Suzuki, Y. Segawa, K. Nozaki, *J. Am. Chem. Soc.* **2007**, *129*, 9570 – 9571; b) Y. Segawa, Y. Suzuki, M. Yamashita, K. Nozaki, *J. Am. Chem. Soc.* **2008**, *130*, 16069 – 16079; c) J. Monot, A. Solovyev, H. Bonin-Dubarle, É. Derat, D. P. Curran, M. Robert, L. Fensterbank, M. Malacria, E. Lacôte, *Angew. Chem. Int. Ed.* **2010**, *49*, 9166 – 9169; *Angew. Chem.* **2010**, *122*, 9352 – 9355; d) M. Sajid, G. Kehr, C. G. Daniliuc, G. Erker, *Angew. Chem. Int. Ed.* **2014**, *53*, 1118 – 1121; *Angew. Chem.* **2014**, *126*, 1136 – 1139.

[3] H. Noda, G. Erős, J. W. Bode, *J. Am. Chem. Soc.* **2014**, *136*, 5611 – 5614.

[4] G. A. Molander, J. Raushel, N. M. Ellis, *J. Org. Chem.* **2010**, *75*, 4304 – 4306.

[5] A. M. Dumas, J. W. Bode, *Org. Lett.* **2012**, *14*, 2138 – 2141.

[6] H. Noda, J. W. Bode, manuscript submitted.

[7] a) Z. He, P. Trinchera, S. Adachi, J. D. St. Denis, A. K. Yudin, *Angew. Chem. Int. Ed.* **2012**, *51*, 11092 – 11096; *Angew. Chem.* **2012**, *124*, 11254 – 11258; b) Z. He, A. Zajdlik, A. K. Yudin, *Acc. Chem. Res.* **2014**, *47*, 1029 – 1040.

[8] a) D. Tilly, F. Chevallier, F. Mongin, P. C. Gros, *Chem. Rev.* **2014**, *114*, 1207 – 1257; b) H. J. Reich, *Chem. Rev.* **2013**, *113*, 7130 – 7178; c) J. Clayden in *Organolithiums: Selectivity for Synthesis* Tetrahedron Organic Chemistry, *Vol. 23*, Pergamon Press, Oxford, **2002**.

[9] Preparation of organotrifluoroborate salts under non-etching conditions: A. J. J. Lennox, G. C. Lloyd-Jones, *Angew. Chem. Int. Ed.* **2012**, *51*, 9385 – 9388; *Angew. Chem.* **2012**, *124*, 9519 – 9522.

[10] E. Bernhardt, M. Finze, H. Willner, *Z. Anorg. Allg. Chem.* **2003**, *629*, 1229 – 1234.

[11] a) B. Bánhidai, U. Schöllkopf, *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 836 – 837; *Angew. Chem.* **1973**, *85*, 861 – 862; b) R. R. Fraser, P. R. Hubert, *Can. J. Chem.* **1974**, *52*, 185 – 187; c) K. Smith, K. Swaminathan, *J. Chem. Soc. Chem. Commun.* **1976**, 387 – 388; d) A. S. Fletcher, K. Smith, K. Swaminathan, *J. Chem. Soc. Perkin Trans. 1* **1977**, 1881 – 1883; e) J. T. Reeves, Z. Tan, M. A. Herbage, Z. S. Han, M. A. Marsini, Z. Li, G. Li, Y. Xu, K. R. Fandrick, N. C. Gonnella, S. Campbell, S. Ma, N. Grinberg, H. Lee, B. Z. Lu, C. H. Senanayake, *J. Am. Chem. Soc.* **2013**, *135*, 5565 – 5568.

[12] a) D. Enders, D. Seebach, *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 1014 – 1015; *Angew. Chem.* **1973**, *85*, 1104; b) D. Seebach, W. Lubosch, D. Enders, *Chem. Ber.* **1976**, *109*, 1309 – 1323.

[13] K. A. Jørgensen, A. B. A. G. Ghattas, S.-O. Lawesson, *Tetrahedron* **1982**, *38*, 1163 – 1168.

[14] a) G. A. Olah, G. K. S. Prakash, M. Arvanaghi, *Synthesis* **1984**, 228 – 230; b) Y. Tominaga, S. Kohra, A. Hosomi, *Tetrahedron Lett.* **1987**, *28*, 1529 – 1531.

[15] a) Y. Mutoh, T. Murai, *Org. Lett.* **2003**, *5*, 1361 – 1364; b) Y. Mutoh, T. Murai, S. Yamago, *J. Am. Chem. Soc.* **2004**, *126*, 16696 – 16697; c) T. Murai, Y. Mutoh, *Chem. Lett.* **2012**, *41*, 2 – 8; d) T. Mukaiyama, T. Yamaguchi, H. Nohira, *Bull. Chem. Soc. Jpn.* **1965**, *38*, 2107 – 2110.

[16] R. A. Batey, T. D. Quach, *Tetrahedron Lett.* **2001**, *42*, 9099 – 9103.

[17] X. Wang, P. Rabbat, P. O'Shea, R. Tillyer, E. J. J. Grabowski, P. J. Reider, *Tetrahedron Lett.* **2000**, *41*, 4335 – 4338.

[18] A. J. J. Lennox in *Organotrifluoroborate Preparation, Coupling and Hydrolysis*, Springer Theses, Springer, **2013**, pp. 11 – 36.

