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Scalable Synthesis of the VEGF-R2 Kinase Inhibitor JNJ-17029259 Using Ultrasound-Mediated Addition of MeLi−$CeCl_3$ to a Nitrile

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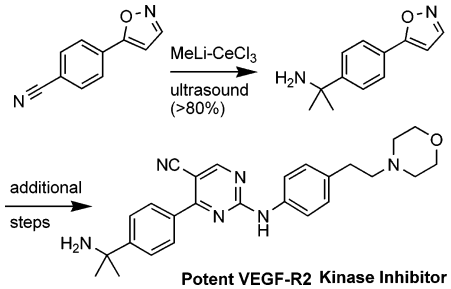
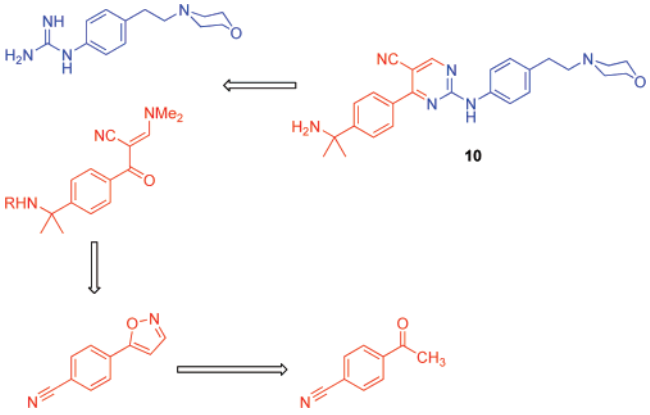


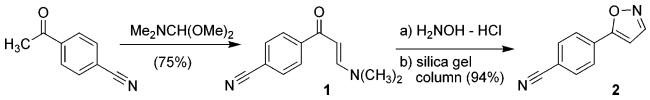
The preparation of the selective VEGF-R2 kinase inhibitor **10** (JNJ-17029259) is described in which the key precursor, 4-(5-isoxazolyl)benzonitrile, undergoes clean transformation to the corresponding cumylamine derivative with $CeCl_3$−MeLi in THF. This high-yielding cerium mediated transformation is robust, reproducible, and readily scalable based on a requirement for the anhydrous $CeCl_3$ to be milled and subjected to ultrasound treatment prior to addition of methyllithium.

Pyrimidinecarbonitrile derivative (**10**) is a promising anti-angiogenic lead as a potent inhibitor of VEGF-R2 kinase. This compound exhibits significant oral activity in suppressing tumor growth in murine models and is also a potent inhibitor of corneal neovascularization in vivo.[1,2] The synthesis of this target presented a unique challenge in that it contained a 2-aminopyrimidine-5-carbonitrile bearing a dimethylbenzyl amine (cumylamine) group. A retrosynthetic analysis (Scheme 1) shows the construction of the pyrimidine unit by condensation of the appropriate guanidine and acrylonitrile derivatives; this acrylonitrile is derived from an isoxazole.[3] While the isoxazole is easily prepared from commercially available 4-acetylbenzonitrile (Scheme 2),[4] the conversion of the nitrile to the required benzyl amine is especially problematic because of the sensitivity of the isoxazole to base.

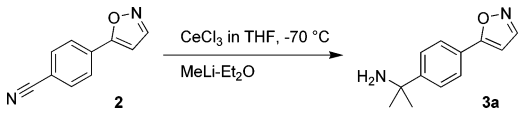
SCHEME 1. Retrosynthetic Analysis



SCHEME 2. Preparation of 4-(5-Isoxazolyl)benzonitrile



SCHEME 3. Addition of MeLi−$CeCl_3$ to 4-(5-Isoxazolyl)benzonitrile



The use of organocerium reagents appeared to be appropriate as the double addition of these reagents to nitriles had been reported.[5] Under the standard conditions for preparing and using these reagents, the use of MeLi−$CeCl_3$ (Scheme 3) was routinely proven to be inconsistent and variable yields (0 to 95% isolated crude product) were observed. The results were independent of whether the anhydrous $CeCl_3$ was generated from the heptahydrate or the commercially available anhydrous reagent. In cases where poor results were obtained, the reaction mixture usually became a bright yellow color and the product amine was often accompanied by unidentified solid impurities.

The reason for the inconsistent results obtained in our initial runs is not proven, but it is most likely due to incomplete activation of $CeCl_3$ and subsequent incomplete formation of the MeLi−$CeCl_3$ complex. Sonication has been described as an alternative method to facilitate the addition of organocerium reagents to carbonyl compounds.[6] In the reported study, the

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(4) (a) Garcia, E. E.; Benjamin, L. E.; Fryer, R. I. *J. Heterocycl. Chem.* **1974**, *11*, 275. (b) Lin, Y-I.; Lang, S. A., Jr. *J. Heterocycl. Chem.* **1977**, *14*, 345. (c) Lin, Y.-I.; Lang, S. A., Jr. *J. Org. Chem.* **1980**, *45*, 4857. (d) Swain, C. J.; Teran, A.; Maroto, M.; Cabello, A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6058.

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TABLE 1. Addition of MeLi−$CeCl_3$ to 4-(5-Isoxazolyl)benzonitrile[a]

entry	isoxazole (g)	sonication time (h)	$CeCl_3$ (g)	yield (%)	footnote
1	5.75	none	25	0	*b*
2	5.75	2	25	30	*b*
3	5.75	4	25	95	*b*
4	5.75	5.5	25	45	*b*
5	5.75	5	25	47	*b*
6	10.87	4	47.13	83	*c*
7	44.85	21	195	100	*d*
8	68.6	43	298.4	100	*d, e*

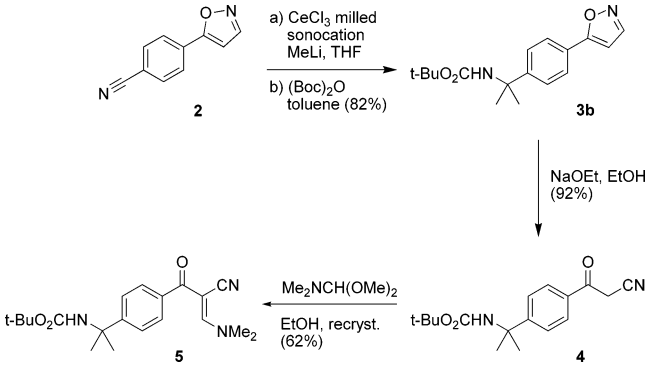
[a] $CeCl_3$−MeLi complex was formed by addition of 0.85 mol of freshly titrated MeLi−Et_2O to each mol of $CeCl_3$. The product purity was >80% by NMR unless otherwise stated. [b] $CeCl_3$ as 10 mesh beads with magnetic stirring. [c] Milled $CeCl_3$ with magnetic stirring. [d] Milled $CeCl_3$ with sonication and simultaneous overhead stirring. [e] For runs of this scale, the results were unchanged with stirring and sonication times between 16 and 48 h.

$CeCl_3$−THF mixture was sonicated for 1 h prior to cooling the suspension and generating the organocerium complex leading to 77% to 97% isolated yields of the addition product for the examples reported. In a subsequent report, $CeCl_3$ sonication was used in the addition of MeLi−$CeCl_3$ to a nitrile during the preparation of the (*R*)-3-(1-amino-1-methylethyl)pyrrolidine group of the antiinfective agent PD-138312.[7] Sonication was shown to be important to aid in the addition of organocerium reagents to carbonyl groups and may also be important for cerium-mediated additions to the nitrile group. While encouraged by these examples, there was no report of this addition in the presence of the strongly sensitive isoxazole. Nevertheless, it is clear that sonication should, at a minimum, help to keep the $CeCl_3$ more finely suspended in THF facilitating its activation.

In our work, commercially available anhydrous $CeCl_3$ (10 mesh beads) was preferred over the heptahydrate because the drying step was eliminated.[8] Examination of representative runs (Table 1) indicates that little product was isolated when the $CeCl_3$ suspension was stirred magnetically prior to methyllithium addition (entry 1). When the $CeCl_3$ in THF was initially sonicated prior to methyllithium addition, the yields improved, but inconsistent results were still obtained (entries 2−5). It is possible that these results were due to nonuniform or excessively large $CeCl_3$ particle size obtained even after the sonication of the commercial reagent. The magnetic stirring used in these runs may be inadequate to fully suspend the $CeCl_3$. The net result of this situation would be the presence of excess methyllithium to the extent that a substantial portion of the $CeCl_3$ was unavailable to react. To address this possibility, instead of using 10 mesh anhydrous $CeCl_3$, this reagent was ground to a fine powder using a commercial household coffee bean grinder. The grinding operation was carried out in a nitrogen-flushed glovebag and the $CeCl_3$ powder was transferred to a flask in the glovebag.

The initial run (entry 6) with finely ground and sonicated $CeCl_3$ appeared to address the inconsistent results for entries

SCHEME 4



2−5 and was encouraging. Magnetic stirring became impractical as the reaction scale was increased; for a run attempted using 17 g of nitrile **2** and 74 g of $CeCl_3$, the mixture could no longer be stirred reliably using magnetic means even though the $CeCl_3$ had been milled prior to the start of the run. Additionally, commercial $CeCl_3$ in THF is a heavy suspension that needs strong stirring to prevent it from settling. For larger scale runs, magnetic stirring was changed to overhead stirring to ensure that the $CeCl_3$ would remain well suspended during the reaction (entries 7 and 8). This change also allowed for simultaneous stirring and sonication operations.

Typically, large-scale runs were set up to sonicate and stir for 16 h (overnight); stirring and sonication times longer than this were not detrimental to the product yield or purity. In all cases, when the mixture was stirred and sonicated, a quantitative yield of the amine was obtained and product purity was high (>80%, NMR estimate). The reaction noted in entry 8 was performed several times on the scale indicated; the scale up was limited by the size of the reaction flask (5 L) that could be placed into the sonicator. The color of the reaction mixture typically became faint yellow during or after the addition of methyllithium. These runs invariably led to good conversion to the desired product. In runs where the reaction picked up a pronounced deep yellow color[9] during the addition, the yield was poor or the reaction failed completely. This observation was more common for the initial magnetically stirred runs and not typical for those done with combined overhead stirring and sonication.

With a proven method for the preparation of the desired benzylamine **3a**, this compound was converted immediately into the Boc derivative **3b** (Scheme 4). The yield of **3b** over both steps was 82%. The isoxazole was opened with $NaOC_2H_5$ to give cyanoketone **4** (92%); this was next converted into acrylonitrile **5** (62%). Guanidine **8** was prepared from commercially available 4-nitrophenylethyl alcohol (Scheme 5). This alcohol was coupled to morpholine through the corresponding mesylate intermediate.[10] Reduction of the nitro group provided aniline **7**,[11] which was finally converted to guanidine **8** by treatment with 3,5-dimethylpyrazole-1-carboxamidine nitrate (90 °C) for 1 h (43%).[12]

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(7) (a) Fedij, V.; Lenoir, E. A., III; Suto, M. J.; Zeller, J. R.; Wemple, J. *Tetrahedron*: *Asymmetry* **1994**, *5*, 1131. To the best of our knowledge, prior to this report, there were no examples of sonication-assisted addition of MeLi−$CeCl_3$ to nitriles. These authors did not indicate whether sonication altered the yield, purity, or percent ee of their product. (b) After our work was completed an alternate method for $CeCl_3$ activation was reported: Limanto, J.; Dorner, B.; Devine, P. N. *Synthesis*, **2006**, 4143.

(8) Takeda, N.; Imamoto, T. In *Organic Synthesis*; Martin, S. F., Ed.; John Wiley & Sons, Inc.: New York, 1999; Vol. 76, p 228.

(9) Incomplete or improperly dried $CeCl_3$ has been known to cause yellow gummy reaction mixtures, see: Dimitrov, V.; Kostova, K.; Genov, M. *Tetrahedron Lett.* **1996**, *37*, 6787.

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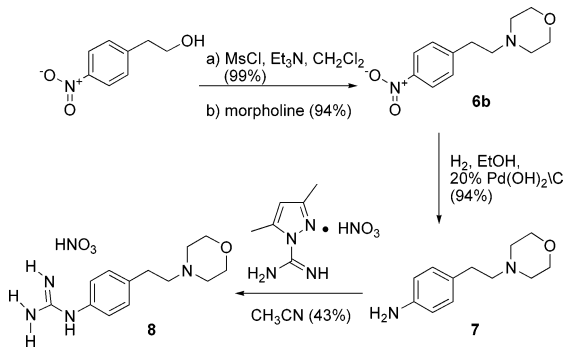
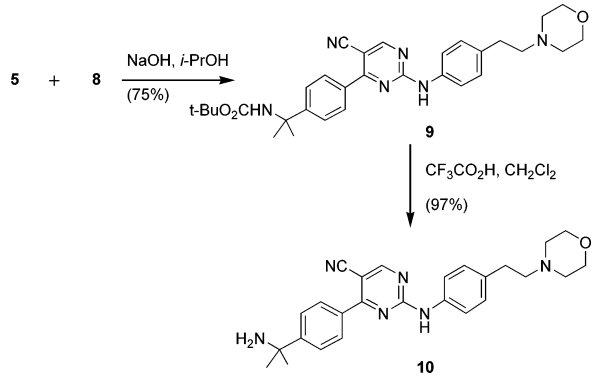
SCHEME 5



SCHEME 6



As shown in Scheme 6, coupling of acrylonitrile **5** with guanidine nitrate **8** was accomplished by heating the components in 2-propanol in the presence of NaOH to give **9** (75%); deprotection using TFA provided the target pyrimidine **10** (97%). This product was crystallized (EtOH) to give a 79% isolated yield that was increased to 97% by additional material provided from the mother liquors.

An efficient synthesis of VEGF-R2 kinase inhibitor **10** has been described in which the pivotal step in the reaction sequence was a stirred-ultrasound-assisted cerium-mediated preparation of a key cumyl amine intermediate **3a**. The ultrasound modification has made this step highly dependable and easily scaled to provide approximately 80 g per run in a 5-L reaction flask. The modification to Ciganek's method[5] described in this report for the MeLi−$CeCl_3$ addition to a nitrile requires no special equipment and should have applicability to other substrates.

Experimental Section

Starting materials, reagents, and solvents obtained from commercial suppliers were used without any purification. Methyllithium in ether was assayed before use as described in the literature (Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.*, **1976**, *41*, 1879).

General Procedure for MeLi−$CeCl_3$ Addition to 4-(5-Isoxazolyl)benzonitrile (2) To Give 3a. Preparation of cerium(III) chloride: Anhydrous $CeCl_3$ (99.9%), supplied as 10 mesh beads (packaged in ampules), was ground in a coffee bean grinder in a nitrogen-filled glovebag. For a run requiring 300 g of $CeCl_3$, the reagent was ground in 100−150 g portions for 1 min and then transferred to a dry, nitrogen-flushed 500-mL single-neck round-bottom flask inside the glovebag. After the entire portion of the reagent was ground, the flask was sealed with a septum, removed from the glovebag, and weighed.

Preparation of the $CeCl_3$−THF complex: The anhydrous $CeCl_3$ powder (298.4 g, 1.21 mol) prepared above was transferred to a dry, nitrogen-flushed 5-L 4-neck Morton flask equipped with an overhead stirrer, nitrogen inlet adapter, thermocouple, and septum. After the transfer, the flask was evacuated and filled with nitrogen (3×) and cooled in an ice−water bath for 30 min, then anhydrous THF (1.85 kg) was added to the stirred solid by cannula. After the THF addition, the cooling bath was removed and replaced by a sonicator. The mixture was sonicated continuously while stirring typically for 16−48 h.

Representative run: After the sonication with stirring, the sonicator was removed and the mixture cooled to an internal temperature of less than −75 °C. After this point was reached, freshly titrated MeLi (1.57 M, 655 mL, 1.03 mol) in ether was added using a gastight 100-mL syringe. The resulting pale yellow mixture was stirred for 1 h at <−75 °C. A solution of isoxazole **2** (68.6 g, 0.403 mol) in anhydrous THF (1.29 kg) was added to the cold $CeCl_3$−MeLi mixture over 0.75 h via cannula. After the reaction was stirred at −75 °C for 1 h, the cooling bath was removed and the mixture was allowed to warm to 0 °C over 1 h. This mixture was re-cooled to −75 °C prior to workup.

Workup: A 22-L, 4-neck Morton flask equipped with an overhead stirrer, nitrogen inlet adapter, stopper, and a $^1/_4$ in. ID Teflon tube was charged with EtOAc (3 L) and concentrated NH_4OH (1 L). The above reaction mixture at −75 °C was transferred into the stirred flask containing EtOAc and NH_4OH with a slight nitrogen pressure and vacuum using the Teflon tube. After the transfer was completed, the reaction flask was rinsed with additional EtOAc (2 × 1.5 L). The combined EtOAc solution was filtered and dried overnight with Na_2SO_4 (500 g). The solution was filtered and concentrated in vacuo using a diaphragm pump (20−25 IHg) with the bath maintained near room temperature. After most of the solvent was removed, the pump was changed to a high-vacuum pump (25−28 IHg) and the bath temperature was increased to 30 °C. The mixture was allowed to cool to give 86 g (>100%) of **3a** as a light yellow oil. ^{1}H NMR ($CDCl_3$) indicated that the product was about 90+% pure. The product was used immediately in the next step without any purification. MS: $[MH]^+$ 203. ^{1}H NMR ($CDCl_3$): δ 8.30 (d, 1H, J = 1.9 Hz), 7.77 (d, 2H, J = 8.6 Hz), 7.64 (d, 2H, J = 8.6 Hz), 6.50 (d, 1H, J = 1.9 Hz), 1.55 (br s, 2H), 1.50 (s, 6H).

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Supporting Information Available: Experimental details for the preparation of compounds **1**, **2**, and **3b**−**10** and spectral characterization data for compounds **3a**−**5** and **8**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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