Preparation of a key intermediate en route to the anti-HIV drug lenacapavir

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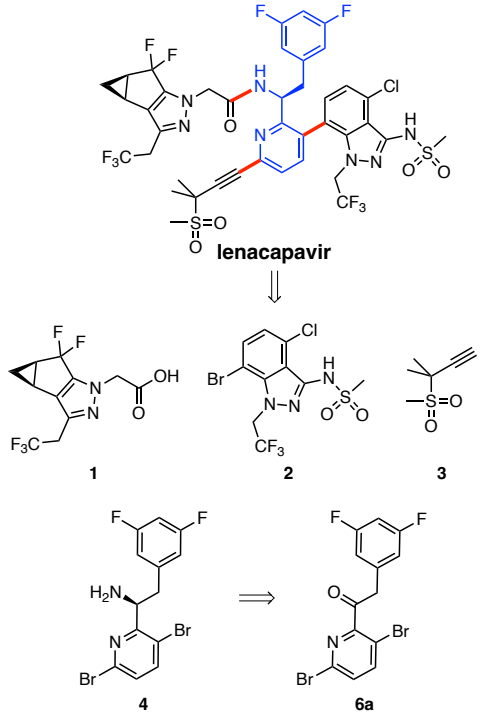
ABSTRACT: A very efficient 4-step synthesis of the main fragment of Gilead's anti-HIV drug lenacapavir is described. The route showcases a 1,2-addition to an intermediate aldehyde using an organozinc halide derived from a commercially available difluorobenzyl Grignard reagent. This sets the stage for oxidation of the resulting secondary alcohol to the desired ketone which relies solely on catalytic amounts of TEMPO together with NaClO as terminal oxidant, affording the targeted ketone in 67% overall yield.

Introduction

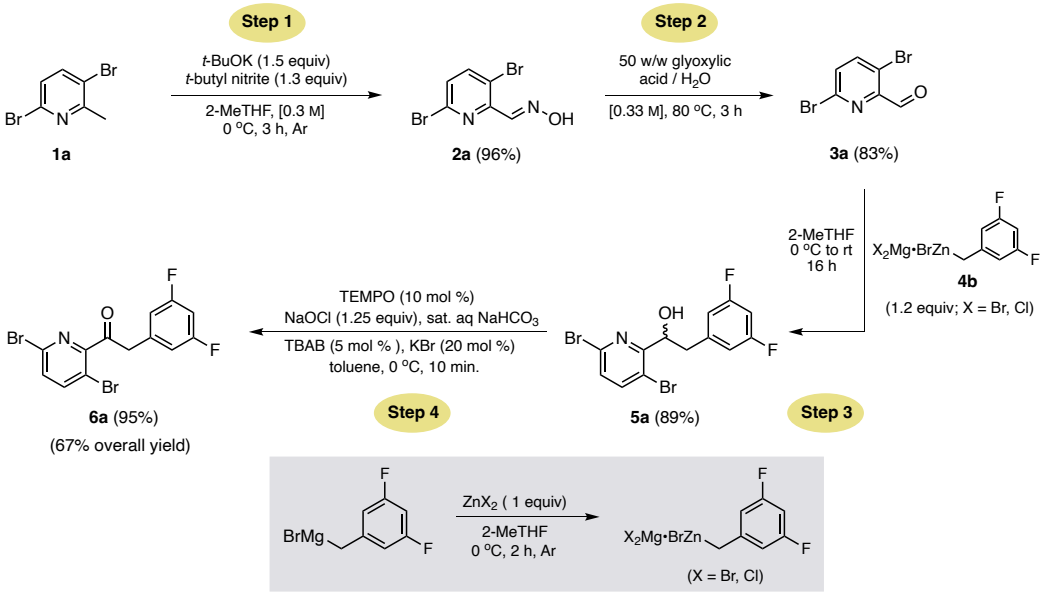
The Human Immunodeficiency Virus (HIV) and its progression to acquired immunodeficiency syndrome (AIDS),[1] has claimed the lives of millions of people worldwide since the early 1980's.[2] It has been estimated that about 86 million people have been infected worldwide resulting in a 47% mortality rate.[3] Since the start of this epidemic, many advancements have been made leading to treatments that, today, allow individuals infected with HIV to live a longer and healthier life.[2] Nonetheless, as of 2022, 39 million people have still been found HIV positive, with ca. 630,000 people dying from AIDS related illnesses; most cases are localized in selected regions of eastern and southern Africa.[4] Several treatments have been developed that minimize the frequency of medication (*i.e.,* associated with pills or injections) thereby reducing risk to the patient.[5] In 2021, the FDA approved Cabenuva, the first of its kind as an extended release HIV treatment requiring only 1 dose every 1 to 2 months (via injection) of a suspension containing both cabotegravir and rilpivirine.[6] A year later, the FDA approved Gilead's lenacapavir (Scheme 1), sold as Sunlenca. Lenacapavir is a potent two-dose treatment given only once a year for HIV-1 positive patients, found to be up to 83% effective in patient improvement.[7] This drug functions as capsid inhibitor preventing the virus from reproducing, a novel mechanism of action for this type of treatment.[8] Offered as a tablet or injection, lenacapavir has projected sales as high as $1.6 billion/year, making it a likely blockbuster drug. Given the effectiveness and hence, anticipated impact of lenacapavir, accessibility by those in low and midddle income (LMIC) countries becomes a high priority. This, ultimately, translates into cost, an issue that can be accommodated, in large measure, by the synthetic route used to produce this drug. Retrosynthetic analysis indicates that lenacapavir is composed of four main fragments (Scheme 1).[9]

Scheme 1. Retrosynthetic analysis of lenacapavir



Intermediate **4** represents the highly functionalized core of the molecule to which the additional components can be introduced via a Sonogashira reaction associated with the alkyne, a Suzuki-Miyaura coupling that inserts the benzpyrazole moiety, and an amide-forming process for insertion of the nonracemic carboxylic acid **1**.

Scheme 2. 4-Step synthesis of ketone 6



Efforts were set towards developing a cost effective synthesis of ketone **6a**, a likely precursor to **4**. To the best of our knowledge there is no openly available route to ketone **6a**. Herein, therefore, we describe a novel 4-step sequence to this key, central component of lenacapavir that proceeds in 67% overall yield (Scheme 2).

Results and Discussion

Initial efforts focused on use of 3,6-dibromopicolinic acid (**1b**) as starting material, en route to Weinreb amide **2b**, anticipating addition of commercially available 3,5-difluorobenzylmagnesium bromide (**4a**) to afford ketone **6a** in a two-step fashion (Scheme 3).[10,11] Weinreb amide **2b** was prepared in moderate yields of 77% and 83% using thionyl chloride[12] and T3P,[13] respectively. Introduction of the commercially available Grignard **4a** in 2-MeTHF, however, led to only trace amounts of ketone **6a**. Aside from lack of efficiency observed in this transformation, and since the cost of acid **1b** is quite high, this route was abandoned in favor of a far more attractive sequence using the corresponding picoline analog **1a** (Table 1).[14]

Starting from inexpensive commercially available 3,6-dibromo-2-methylpyridine **1a**, oximation cleanly leads to oxime **2a** in excellent yield (96%) using recyclable 2-MeTHF.[15] Hydrolysis of **2a** in the presence of 50 wt % glyoxylic acid effectively generates aldehyde **3a** (Scheme 2). 1,2-Addition of the derived zinc halide **4b**, generated from benzylic Grignard **4a** in 2-MeTHF[15] to aldehyde **3a** led to alcohol **5a**. Lastly, oxidation of **5a** to ketone **6a** was smoothly accomplished in minutes at 0-5 °C using catalytic TEMPO and a slight excess of NaClO in a biphasic mixture (Scheme 2).

Synthesis of aldehyde 3a. This followed a literature procedure,[9] involving a 2-step route starting from 3,6-dibromo2-methylpyridine. Initial screening of the oximation in anhydrous THF in the presence of *t*-butylnitrite (TBN) and potassium *t*-butoxide as base (1 equiv) at 0 °C to rt resulted in no reaction (Table 1, entry 1). Increasing the amount of base to 1.5 equiv led to some of the desired product, albeit in poor yield (ca. 11%; entry 2). However, by changing the order of addition a far better reaction resulted (entry 3). That is, adding **1a** along with TBN in THF followed by the dropwise addition of a solution of *t*-BuOK in THF increased the yield to ca. 45% (entry 3). Finally, it was found that not only a dropwise addition of the base but also maintaining the temperature at 0 °C was crucial (entries 4-6). Both THF and 2-MeTHF performed equally well, however, we opted to carry out this transformation in 2-MeTHF, which is a preferred green solvent.[15] Upon quenching this reaction with sat. aqueous NH_4Cl, the solvent can easily be recovered to the extent of 85-89%, and then reused (SI, S4). The crystalline nature of oxime **2a** allowed for a simple filtration, followed by several water washes after which the material could be used in the next step (SI, S5). Several acids were then screened under aqueous conditions (SI, Table S2). Ultimately, oxime **2a** was best hydrolyzed using 50% w/w glyoxylic acid/H_2O at 80 °C over three hours, leading to aldehyde **3a** in 83% yield. This hydrolysis leading to **3a** required only a simple filtration, followed by water washes to obtain relatively pure material (99% pure, by ^1H NMR).

Scheme 3. Synthesis of ketone 6a via Weinreb amide 2b

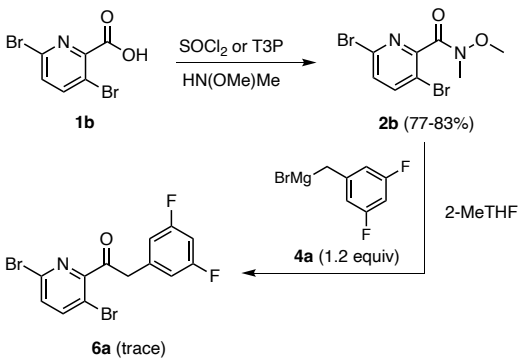
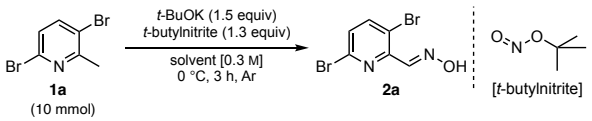


Table 1. Optimization of step 1.



entry	KO*t*-Bu (equiv)	addition order	temperature	yield[a]
1[d]	1.0	KO*t*Bu, then *t*-butylnitrite	0 °C to rt	NR
2[d]	1.5	KO*t*Bu, then *t*-butylnitrite	0 °C to rt	11%
3[d]	1.5	*t*-butylnitrite, then KO*t*-Bu dropwise	0 °C to rt	45%
4[d]	1.5	*t*-butylnitrite, then KO*t*-Bu dropwise	keep at 0 °C	93%
5e	**1.5**	***t*-butylnitrite, then KO*t*-Bu dropwise**	keep at 0 °C	**94%[b]**
6e	**1.5**	***t*-butylnitrite, then KO*t*-Bu dropwise**	keep at 0 °C	**96%[c]**

a) Isolated yield. b) Run on a 40 mmol scale. c) Run on a 20 mmol scale. d) THF was used as solvent. e) 2-MeTHF was used as solvent

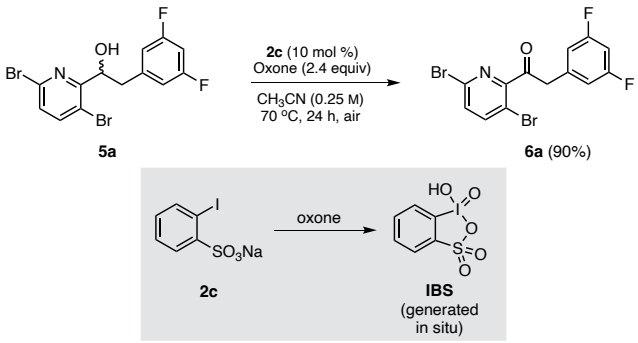
Synthesis of alcohol 5a. Alcohol **5a** was anticipated to form via a 1,2-addition of Grignard **4a**. Optimization revealed two major side products **5b** and **5c**, the former being favored (Table 2, entries 1-2). Due to the high reactivity of Grignard **4a** in combination with the highly activated position-6 on aldehyde **3a**, a competing S_NAr reaction led to by-product **5b**. To minimize this undesired material, temperature, stoichiometry, as well as order of addition were probed (see SI, Table S3) with little improvement observed. To increase electrophilicity of the carbonyl carbon, a Lewis acid ($BF_3 \bullet OEt_2$) was introduced; however, only 56% conversion was noted of which 50% selectivity for the 1,2-addition product was formed along with 38% of the S_NAr product and 11% of alcohol **5c** (entry 5).

Among efforts to decrease side product formation (**5b** and **5c**) use of CuCN and zinc salts were added to Grignard **4a** to form the less reactive cyanocuprate and zinc halide species, respectively. Use of CuCN was ineffective, leading to only 43% 5a along with 36% of 5b and 6% of 5c (entry 6). The organozinc reagent was prepared from zinc dust and difluorobenzyl bromide. However, 27% of side product 5b was obtained (entry 7). Interesting, however, side product 5c was not observed. A screening of zinc salts (e.g., $ZnBr_2$) added to Grignard **4a** gratifyingly resulted in a decrease in formation of **5b** (<6%) and only ca. 2-3% of **5c**.[16] This indicated that the zinc halide complex should be generated by adding one equivalent of zinc salt to a solution of benzyl Grignard **4a** in 2-MeTHF. This new solution was then used to selectively carry out 1,2-addition onto aldehyde **3a** generating alcohol **5a**. When performed in this fashion, an 88% yield of 5a was obtained, while minimizing side product formation (entry 9). Furthermore, in efforts to further lower the overall cost, use of $ZnCl_2$ in place of $ZnBr_2$ showed similar results (89%; entry 10).[17]

Oxidation of alcohol 5a to ketone 6a. Once alcohol **5a** was efficiently in hand, attention turned towards finding an efficient oxidation en route to ketone **6a**. The first focused on stoichiometric amounts of a hypervalent iodide species[18] notwithstanding their potentially explosive nature.[19] In our search (see SI, Table S4) the majority of reagents and conditions screened led to little-to-no conversion. Eventually, using sodium 2-iodobenzenesulfonate (10 mol %) along with Oxone®[20] in acetonitrile (generating IBS *in situ*) gave **6a** in 90% yield[21] (Scheme 4). Notwithstanding the efficiency of this transformation, we envisioned that an even more facile, green, and inexpensive method could be found. Further study led to evaluation of nitroxyl radical catalysts (Figure 1), as these are well known for oxidation of a wide range of primary and secondary alcohols. [22,23] Among these *N*-oxyl catalysts, 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO) stands out as the most available and likely the most cost-effective option. However, the presence of bulky groups (i.e., tetramethyl) adjacent to the active site suggested that steric effects might lower its catalytic activity, particularly in the case of hindered alcohols.[22e] Consequently, alternative *N*-oxyl catalysts have emerged in the past decade mainly aiming to overcome this potential barrier.[22e,24]

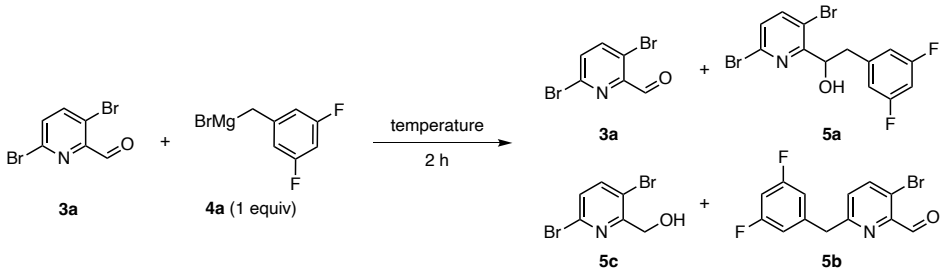
Preliminary studies using *N*-oxyl radical catalysts for this oxidation involved screening based on steric factors present in these systems. Both AZADO and ABNO were examined; initially leading to no reaction in most cases. Using a hypervalent iodine species such as diacetoxyiodobenzene (PIDA), or oxygen gas as the stoichiometric oxidant in combination with either TEMPO or AZADO, the latter in combination with sodium hypochlorite (NaClO) in a biphasic solvent system (H_2O : DCM) gave some oxidation. Worth noting is the crucial role temperature plays in this transformation. That is, for temperatures of 22 °C and above no product formation was observed even with relatively high loadings of catalyst. Furthermore, in addition to maintaining the temperature at 0 °C, the reaction time required close monitoring. When this transformation was carried out at 0 °C for a period of one hour, only 40% product was observed via qNMR. But when the reaction time was reduced to *ca.* eight minutes, a 70% yield of ketone **6a** was observed (also by qNMR). Apparently, this transformation is much more efficient at colder temperatures (*ca.* 0 °C), likely due to the short lifetime of in situ-generated hypobromous acid and the instability of the oxonium species containing the *N*-oxyl catalyst at room temperature.[22c] Extended reaction times and amount of oxidant presumably leads to over-oxidation, and/or decomposition of **6a** (SI, Table S5).

Scheme 4. Initial oxidation of 5a to ketone 6a



Continued investigation indicated that reducing the amount of NaClO could minimize side product formation. A thorough screening of oxidant was carried out confirming the existence of products of over-oxidation/decomposition, thereby decreasing the resulting yield of **6a** (SI, Table S6). Attempts were then made to find an alternative, potentially recoverable solvent and avoid using the common and generally accepted organic solvent for this type of oxidation such as environmentally egregious DCM.[25] Screening solvents led to the potential for toluene and ethyl acetate to serve as good replacements for DCM (SI, Table S7). Re-optimization of the loading of NaClO using toluene (SI, Table S8) indicated that approximately 1.25 equivalents of a 10-15% aq. NaClO in 0.2 M toluene led to a nearly quantitative yield in ten minutes at 0 °C, with 97% purity by HPLC without any further purification (Table 3, entry 1).

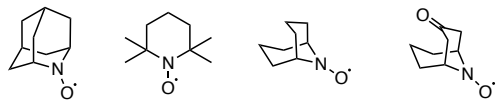
Table 2. Optimization studies leading to product 5a



entry[a]	temperature	conditions	**3a** (%)[c]	**5a** (%)[c]	**5b** (%)[c]	**5c** (%)[c]
1	0 °C to rt	-	11	34	44	3
2	keep at 0 °C	-	9	38	40	6
3	keep at 0 °C	aldehyde : Grignard = 1:1.2	5	14	66	3
4	keep at 0 °C	add Grignard dropwise over 2h	42	10	33	5
5	keep at 0 °C	add 1 equiv BF_3OEt_2	44	27	20	6
6	keep at 0 °C	mix 1 equiv CuCN with Grignard, then use 0.8 equiv	12	43	36	6
7	keep at 0 °C	use organozinc reagent made from bromide and zinc dust	11	60	27	nd
8	0 °C to rt	mix 1 equiv $ZnBr_2$ with Grignard, then use 1.0 equiv mixture, 12 h	15	80	3	2
9	**0 °C to rt**	**mix 1 equiv $ZnBr_2$ with Grignard, then use 1.2 equiv mixture, 12 h**	**8**	**88**	**2**	**1**
10[d]	**0 °C to rt**	**mix 1 equiv $ZnCl_2$ with Grignard, then add solution of 3a dropwise 16 h**	—	**89[b]**	—	—

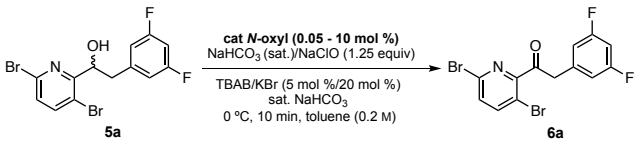
a) Reactions run on a 0.2 mmol scale. b) Isolated yield c) Yield determined by GC-MS using naphthalene as internal standard. d)Reaction was run on a 0.25 mmol scale. For experimental conditions, see SI, S8.

Figure 1. Commonly used nitroxyl radical catalysts



Lastly, optimization of the loading of organocatalyst remained. Screening this reaction variable showed that only 0.25 mol % of highly active AZADO is required for an efficient oxidation of **5a** to **6a** (Table 3, entry 3). Other catalysts, such as the ABNO showed similar efficiency to that seen with AZADO (entry 4). However, 9-azabicyclo[3,3,1]nonan-3-one-9-oxyl (keto-ABNO) was not as active as ABNO (entry 5). Although initial attempts using TEMPO were unsuccessful, this far less costly catalyst was revisited under our newly optimized conditions. Use of 10 mol % TEMPO now gave **6a** in 98% HPLC conversion and 95% purity (entry 6), and thus became the method of choice (Scheme 2, step 4). Reducing the amount of TEMPO in half resulted in only *ca.* 80% conversion (See SI, Table S10). The potential for recycling the reaction medium was also demonstrated, further decreasing the environmental footprint for this key oxidation. That is, following the initial reaction and extraction of the aqueous phase that contains catalyst/TBAB/KBr, a second oxidation was carried out by adding recovered toluene and **5a** resulting in 79% conversion. However, an additional 5 mol % TEMPO and 0.25 equiv NaClO increased the conversion to 90% (SI, S18).

Table 3. Screening of various *N*-oxyl catalysts



entry[e]	catalyst	mol %	conversion to **5a**[a]	**6a** (%)[b]	side product(s) (%)[c]
1[d]	AZADO	1	99	97	2
2	AZADO	0.5	99	93	6
3	AZADO	0.25	96	95	1
4	ABNO	1	99	98	1
5	keto-ABNO	5	52	32	20
6	**TEMPO**	**10**	**98**	**95**	**3**

a) Consumption of **5a** based on HPLC. b) Conversion of **5a** to **6a** based on HPLC. c) Conversion of **5a** to side product/s based on HPLC analysis. d) Run on a 0.25 mmol scale. e) run on a 1 mmol scale

Conclusion

A straightforward and potentially cost-effective synthesis of ketone **6a** has been developed, which is a key component in the synthesis of the potent anti-HIV drug lenacapavir. The approach features a 1,2-addition to an aldehyde that relies on an in situ-generated organozinc halide complex from the commercially available Grignard reagent difluorobenzylmagnesium bromide. Oxidation of the newly formed secondary alcohol **5a** can be effectively carried out using catalytic amounts of TEMPO in the presence of NaClO as terminal oxidant. This 4-step sequence leads, in 67% overall yield, to the targeted intermediate **6a**, a route that has significant potential for scale up.

ASSOCIATED CONTENT

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Author Contributions

J.C.C. contributed to experimental work and writing of the ms and SI. Y.H., E.O., and K.T.M. contributed to experimental and optimization work. BHL oversaw the work and assisted in revising the ms and SI. All authors have given final approval to the final version of the current version of this manuscript.

Notes

The authors declare no competing financial interest.

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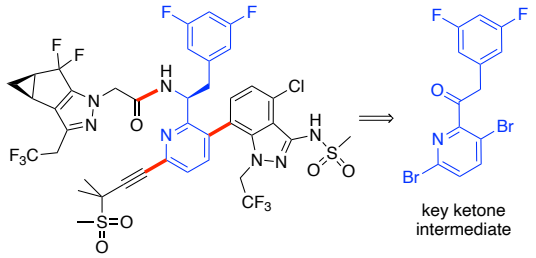
TOC Graphic



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