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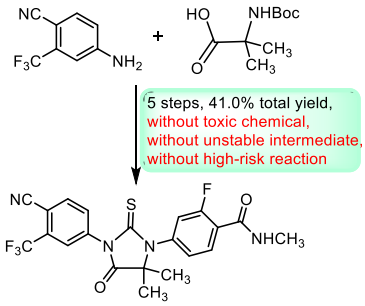
Graphical Abstract



A novel route for synthesis enzalutamide was reported in 41.0% total yield without toxic chemical, unstable intermediate and high-risk reaction. It is a potential efficient and economical procedure for industrialization.

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ABSTRACT

A novel route of enzalutamide was developed in five steps. Starting from 4-amino-2-(trifluoromethyl)benzonitrile (**7**) and Boc-2-aminoisobutyric acid (**16**), condensation, deprotection, Ullmann coupling, cyclization and amination provided enzalutamide in 41.0% total yield. This route avoids the using of toxic chemical, unstable intermediate and high-risk reaction. It is a potential efficient and economical procedure for industrialization.

According to the statistics of the American Cancer Society 2022 [1], the number of prostate cancer (PCa) new cases is estimated at 268,490 in US for 2022. Enzalutamide (**1**, Fig. 1) was the first second-generation non-steroidal androgen receptor (AR) antagonist to be used to treat castration-resistant prostate cancer (CRPC) that had spread or relapsed. Comparing with the first-generation AR antagonists nilutamide [2], flutamide [3] and bicalutamide [4], enzalutamide not only competitively inhibited androgen binding to AR, but also inhibited nuclear translocation of the AR, DNA binding and coactivator recruitment [5,6]. Enzalutamide was approved by FDA in 2012. Furthermore, enzalutamide showed potential therapeutic effect on triple-negative breast cancer with AR high-expression [7-10]. In the future, the requirement of active pharmaceutic ingredient (API) would be further increased. Therefore, it was of great research significance to develop a novel synthetic method of enzalutamide, especially that suitable to industrial production.

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Two feasible routes have been reported for the synthesis of industrial scale enzalutamide. One was undertaken by researchers of Medivation Inc. (Scheme 1) [11], which began with 4-bromo-2-fluorobenzonic acid (**2**). The key intermediate methyl 2-((3-fluoro-4-(methylcarbamoyl)phenyl)-amino)-2-methylpropanoate (**6**) was prepared by chloration, amination, coupling reaction and methylation from starting material **2**. Intermediate **6** reacted with 4-isothiocyanato-2-(trifluoromethyl)benzonitrile (**8**), which was made from 4-amino-2-(trifluoromethyl)benzonitrile (**7**), to obtain target compound **1**. An evident disadvantage of this route was the use of the poisonous reagent iodomethane to prepare the intermediate **6**. Zhou *et al*. [12] made an improvement for this route, but it was difficult to decrease the equivalent of isothiocyanate intermediate **8**. Depending to the high reactivity of isothiocyanate intermediate **8**, leaving group methanol, as a strong nucleophile byproduct of cyclization, could immediately react with **8** to form a typical impurity **9** (Fig. 2). Although impurity **9** could be easily removed by recrystallization with isopropanol, two equivalents of **8** were consumed for the cyclization step, at least.

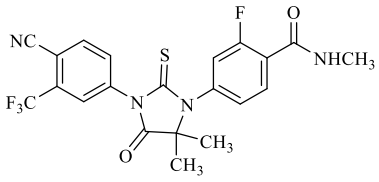

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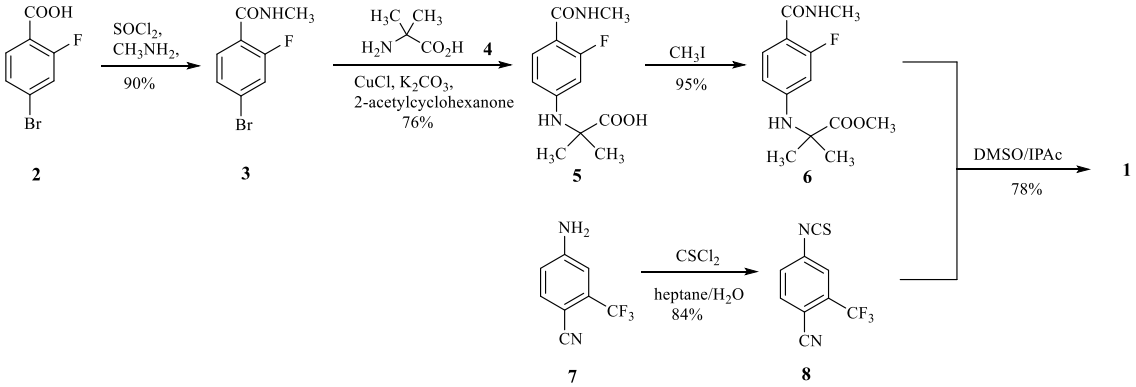
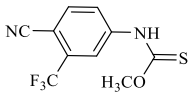
Fig. 1. Structure of enzalutamide (**1**).



Scheme 1. The original route of Medivation Inc. for the synthesis of enzalutamide **1**.

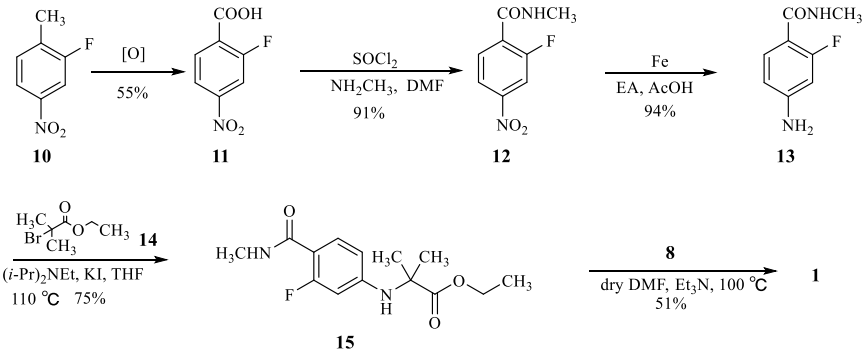


9

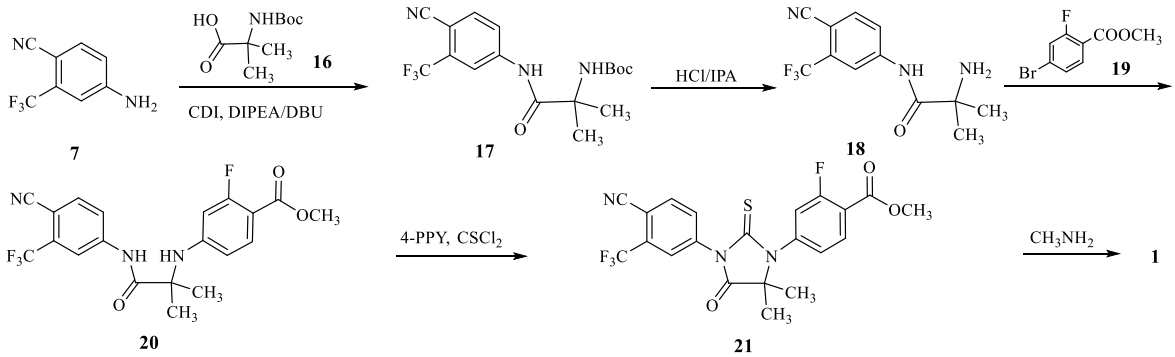
Fig. 2. Typical impurity **9**, by-product of Scheme 1 in cyclization.

An alternative route was reported (Scheme 2) [13,14] to begin with 2-fluoro-4-nitrotoluene (**10**), following by oxidation, chloration, reduction, substitution and cyclization to afford target compound **1**. Although toxic iodomethane was avoided in this route, starting material **10** and intermediates (**11**, **12**) with a nitro group increased the risk of explosion during storage and transportation. Meanwhile, the reduction of **12** with Fe/AcOH or Pb/C-H_2 was a high-risk reaction to synthesize intermediate **13** for industrial scale manufacture. Although API **1** could be obtained by the above routes, several environmentally unfriendly reagents, high-risk reactions and reactive intermediates were still utilized in these routes. Various synthetic strategies have been designed to overcome such disadvantages [15,16], however the low yield and high cost of the overall process limited the practical use of these routes. Thus, a novel synthetic route is urgently needed to develop for the efficient synthesis of **1** with mild condition, stable intermediate and environmentally friendly reagent. Herein we report a new route that highly limits toxic reagents and inconvenient reactive intermediates.

Our new route (Scheme 3) [17] begins with intermediate **7** and Boc-2-aminoisobutyric acid (**16**) to obtain *tert*-butyl (1-((4-cyano-3-(trifluoromethyl)phenyl)amino)-2-methyl-1-oxopropan-2-yl)carbamate (**17**) by condensation. The deprotection of **17** is carried out in the acidic condition to afford 2-amino-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-2-methylpropanamide (**18**). The third step is an Ullmann reaction for the coupling of intermediate **18** with methyl 2-fluoro-4-bromobenzoate (**19**) to give methyl 4-((1-((4-cyano-3-(trifluoromethyl)phenyl)amino)-2-methyl-1-oxopro-pan-2-yl)amino)-2-fluorobenzoate (**20**). Intermediate **20** is reacted with thiophosgene to obtain methyl 4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazoli-din-1-yl)-2-fluorobenzoate (**21**). enzalutamide (**1**) is finally prepared by methylamination of compound **21**.

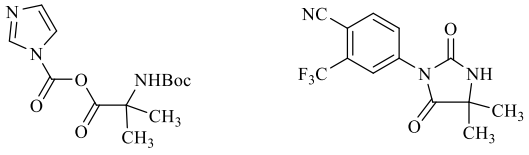


Scheme 2. Alternative route for API **1** manufacture.



Scheme 3. A novel route to synthesize enzalutamide.

Because of the weak nucleophilicity of **7** with two strong withdrawing groups, several conditions were screened with phosphorus oxychloride ($POCl_3$) [18], dicyclohexylcarbodiimide (DCC) [19-22], *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (HATU) [23] and isobutyl chloroformate (IBCF) [24]. Unfortunately, no target compound was found (Table 1, entries 1-5). When 1,1'-carbonyldiimidazole (CDI) was used to activate the carboxy group of starting material **16**, trace amounts of intermediate **17** were found in entries 6 and 7. Because of the poor solubility of Cs_2CO_3 and Na_2CO_3 in THF, we tried to use organic alkali to make a homogeneous reaction such as 4-dimethylaminopyridine (DMAP), 4-methylmorpholine (NMM) and triethylenediamine (DABCO) (entries 8-10). Because of the weak alkaline, we failed to gain the intermediate **17**. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was successfully used to obtain compound **17** in moderate yield by crystallization (entry 11). A typical impurity was found and isolated in the condensation step, with a mass signal $[M + H]^+$ of 298.0. According to the mass result, two possible structures were speculated as reactive intermediate **23** or intramolecular closed ring product **24** (Fig. 3). ^{1}H NMR, ^{13}C NMR and HRMS were used to further identify the structure of this typical impurity (Supporting information). ^{1}H NMR showed signals of aromatic hydrogens and no signal of the Boc protecting group. Therefore, we speculated that the structure of typical impurity was compound **24**. In order to decrease the loss in mother liquid, *N*,*N*-dimethylformamide (DMF) was used instead of tetrahydrofuran (THF) (entry 12). We also found the typical impurity was increasing with the prolonged reaction time. Then the reaction time was shorted from 5 h to 2 h to control the amount of typical impurity (entry 13) and isolate yield was around 75.3%.



23 **24**

Fig. 3. Speculated structures of typical impurity **23** or **24**.

Table 1
Screening of conditions of the condensation step.

Entry	**7**:**16** (molar ratio) [a]	Solvent [b]	Reagent	Base (1.3 equiv.)	Temp. (°C)	Time (h)	Yield (%) [c]
1	1.0:1.1	pyridine	$POCl_3$	DBU	-15~60	5	-
2	1.0:1.1	DMF	DCC	DIPEA	r.t.	1	-
3	1.0:1.1	DMF	DCC/HOBt	DBU	r.t.~60	1	-
4	1.0:1.1	DMF	HATU	DBU	r.t.~100	5	-
5	1.0:1.1	THF	IBCF	DBU	-15~60	5	-
6	1.0:1.1	THF	CDI	DIPEA/Cs_2CO_3	60~65	5	trace
7	1.0:1.1	THF	CDI	DIPEA/Na_2CO_3	60~65	5	trace

8	1.0:1.1	THF	CDI	DIPEA/DMAP	60~65	5	-
9	1.0:1.1	THF	CDI	DIPEA/NMM	60~65	5	-
10	1.0:1.1	THF	CDI	DIPEA/DABCO	60~65	5	-
11	1.0:1.0	THF	CDI	DIPEA/DBU	60~65	5	49.5
12	1.0:1.0	DMF	CDI	DIPEA/DBU	60~65	5	68.5
13	1.0:1.0	DMF	CDI	DIPEA/DBU	60~65	2	75.3

[a] For entries 1-11, the amount of **16** was 0.36 g (1.8 mmol) and for entries 12 and 13, the amount of **16** was increased to 20.0 g (0.11 mol).
[b] For entries 1-11, the solvent volume was 3 mL and for entries 12 and 13, the solvent volume was 60 mL.
[c] Isolated yields.

The deprotection of intermediate **17** was carried out with 4 mol/L HCl in isopropyl alcohol (IPA) [25] or trifluoroacetic acid (TFA) [26] to afford deprotected product **18** with 98.0% or 97.3% yield, respectively. Intermediate **18** was reacted with **19** by Ullmann coupling. Considering the cost of this route, copper sources were utilized as the catalyst in the coupling step [27]. Primarily, copper sources were screened such as copper powder, CuCl, CuBr and CuI (Table 2, entries 1-4) with 2-acetylcyclohexanone and K_2CO_3 in DMF under 120 ℃. Entry 2 showed a better yield at 67.3%. Secondly, we investigated ligands 2-acetylcyclohexanone (entry 2), acetylacetone and *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA) (entries 5 and 6), in which 2-acetylcyclohexanone was still a suitable ligand in the coupling reaction. When this reaction was monitored by thin-layer chromatography (TLC), starting material **7** was found in this system. Therefore, we speculated that the strong basicity or poor stirring condition of K_2CO_3 make compound **18** or **20** hydrolyze. Finally, we screened bases KOAc, *N*,*N*-diisopropylethylamine (DIPEA) and DBU. The stirring conditions were obviously improved, when organic alkali was used (entries 8 and 9), product **20** was obtained in moderate yields (33.3% and 42.9%). The yield was increased to 74.8% when KOAc was used instead of K_2CO_3 (entry 7).

Table 2
Optimization of Ullmann coupling reaction

Entry[a]	Catalyst (0.2 equiv.)	Ligand (0.2 equiv.)	Base (1.3 equiv.)	Time (h)[b]	Yield (%)[c]
1	Cu powder	2-Acetylcyclohexanone	K_2CO_3	6	45.1
2	CuCl	2-Acetylcyclohexanone	K_2CO_3	6	67.3
3	CuBr	2-Acetylcyclohexanone	K_2CO_3	6	48.7
4	CuI	2-Acetylcyclohexanone	K_2CO_3	6	54.5
5	CuCl	Acetylacetone	K_2CO_3	7	52.5
6	CuCl	TMEDA	K_2CO_3	8	22.8
7	CuCl	2-Acetylcyclohexanone	KOAc	7	74.8
8	CuCl	2-Acetylcyclohexanone	DIPEA	9	33.3
9	CuCl	2-Acetylcyclohexanone	DBU	6	42.9

[a.] For entries 1-9, the amount of **18** was 10.0 g and the molar ratio of **18**:**19** was 1:1.2.
[b.] All of the entries were carried in DMF at 120 ℃ (internal temperature), and the reaction time was determined by TLC.
[c.] Isolated yield.

Coupling product **20** was reacted with thiophosgene ($CSCl_2$) or thiophosgene derivatives to construct the thiohydantoin ring. The reaction conditions for cyclization were optimized by the following steps (Table 3). The initial conditions of 1.2 equiv. of thiophosgene and compound **20** in THF or acetonitrile (ACN) (entries 1 and 2) [11] gave only traces of the desired product in entry 2. Increasing the amount of thiophosgene (entry 3) to 3.0 equiv. failed to improve the conversion of intermediate **20**. Because of the formation of byproduct HCl, we screened acid acceptors triethylamine (TEA), DIPEA and DBU (entries 4-6). However, no desired product was found. Notably, when DMAP was used as an acid acceptor, we successfully obtained the cyclization product **21** in 68.2% yield (entry 7). This result showed that DMAP was probably not only used as an acid acceptor, but also as a catalyst for cyclization. Byproduct HCl reacted with DMAP to form a quaternary ammonium salt, which had poor solubility in the solvent and made the stirring condition worse. Mixed alkali including DMAP were screened (entries 8-10) and a 64.7% yield was found with the mixed alkali DIPEA/DMAP. Increasing the proportion of DMAP to 8.0 equiv. improved the yield to 72.4% (entry 11). To further improve stirring conditions, equivalents of thiophosgene and DMAP were decreased to obtain target compound **21** in yield 75.9%-77.5% at lower reaction temperature in order to avoid thiophosgene decomposition (entries 12 and 13). Because cyclization was an intramolecular nucleophilic reaction, the volume of solvent ACN was increased to 40 mL (entry 14). The stirring condition was improved to obtain a 74.3% yield. Non-protonic solvents such as THF and 2-methyltetrahydrofuran (Me-THF) were screened but gave poor yields (entries 15 and 16). 4-Pyrrolidinopyridine (4-PPY), which is a DMAP analogue, was used as an alternative base in cyclization to give a better yield 86.5% (entry 17). 1,1'-Thiocarbonyldiimidazole (TCDI) [28] and phenyl chlorothionocarbonate (ClCSOPh) [29] were investigated to replace the thiophosgene (entries 18-20), which is an environment-unfriendly reagent. The reaction failed with TCDI (entries 17 and 18) and gave only 32.7% of desired product with ClCSOPh (entry 20). When ClCSOPh was used, diphenylthionocarbonate was found as a main byproduct. One molecule of phenol was released by this process, which was still a strong nucleophile and then reacted with another molecule of ClCSOPh to give byproduct diphenylthionocarbonate. This reaction required at less two equivalents of ClCSOPh and the byproduct was hard to remove from the crude product. Finally, we chose the typical condition to scale up to 10g and obtain the desired product in 85.6% yield (entry 21). The last step was an amination, for which we referred to the method reported by Zhou *et al*. [12] to obtain enzalutamide in 86.8% yield.

Table 3
Optimization of the cyclization step.

Entry[a]	Reagent (equiv.)	Solvent (mL)	Mixed alkali (equiv.)	Temp. (℃)	Time (h)	Yield (%)[b]

1	$CSCl_2$ (1.2)	THF (10)	-	reflux	6	-
2	$CSCl_2$ (1.2)	ACN (10)	-	reflux	6	trace
3	$CSCl_2$ (3.0)	ACN (10)	-	reflux	6	trace
4	$CSCl_2$ (3.0)	ACN (10)	TEA (6.0)	40	12	-
5	$CSCl_2$ (3.0)	ACN (10)	DIPEA (6.0)	40	12	-
6	$CSCl_2$ (3.0)	ACN (10)	DBU (6.0)	40	12	-
7	$CSCl_2$ (3.0)	ACN (10)	DMAP (6.0)	40	12	68.2
8	$CSCl_2$ (3.0)	ACN (10)	TEA & DMAP (6.0 & 2.0)	40	12	11.2
9	$CSCl_2$ (3.0)	ACN (10)	DIPEA & DMAP (6.0 & 2.0)	40	12	64.7
10	$CSCl_2$ (3.0)	ACN (10)	DBU & DMAP (6.0 & 2.0)	40	12	21.5
11	$CSCl_2$ (3.0)	ACN (10)	DIPEA & DMAP (6.0 & 8.0)	-10~40	12	72.4
12	$CSCl_2$ (2.0)	ACN (10)	DIPEA & DMAP (4.0 & 6.0)	-10~10	20	77.5
13	$CSCl_2$ (2.0)	ACN (10)	DIPEA & DMAP (4.0 & 2.0)	-10~10	40	75.9
14	$CSCl_2$ (2.0)	ACN (40)	DIPEA & DMAP (4.0 & 6.0)	-10~10	20	74.3
15	$CSCl_2$ (2.0)	THF (10)	DIPEA & DMAP (4.0 & 6.0)	-10~10	20	17.3
16	$CSCl_2$ (2.0)	Me-THF (10)	DIPEA & DMAP (4.0 & 6.0)	-10~10	20	trace
17	$CSCl_2$ (2.0)	ACN (10)	DIPEA & 4-PPY (4.0 & 6.0)	-10~10	20	86.5
18	TCDI (1.5)	ACN (10)	-	reflux	20	-
19	TCDI (1.5)	ACN (10)	DIPEA & DMAP (4.0 & 6.0)	reflux	20	-
20	ClCSOPh (2.0)	ACN (10)	DIPEA & DMAP (4.0 & 6.0)	-10~reflux	20	32.7
21	$CSCl_2$ (2.0)	ACN (10)	DIPEA & 4-PPY (4.0 & 6.0)	-10~10	20	85.6

[a.] For entries 1-19, the amount of **20** (1.0 equiv.) was 1.0 g.
[b.] For entries 1-21, compound **21** was isolated by column chromatography.

In conclusion, a novel route to synthesize enzalutamide was established in five steps including condensation, deprotection, Ullmann coupling, cyclization and amination. Compared with the reported methods, unstable intermediate, toxic chemical and high-risk reaction were avoided in this new route. The purification of intermediate **21** needs to be further optimized. In the future, the challenge in manufacturing enzalutamide would be to completely abandon the use of thiophosgene. Taken together, this approach is a more efficient, convenient and economical route, which provides a new strategy for improving the process of API enzalutamide manufacture.

Acknowledgments

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