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Original article

An improved and practical route for the synthesis of enzalutamide and potential impurities study

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ABSTRACT

An improved and practical synthesis of enzalutamide was accomplished in five steps. Starting from 4-bromo-2-fluoro-benzonic acid, a methyl esterification, Ullmann ligation, methyl esterification, ring closing reaction and final methyl amidation provided the target in 35% total yield with 99.8% purity. Five identified impurities were also synthesized. This efficient and economical procedure avoids the use of highly toxic reagents and multiple recrystallization operations, which is suitable for further industrialization.

1. Introduction

Enzalutamide (**1**, Fig. 1) is a new type of androgen receptor (AR) antagonist [1] that was developed by Medivation Inc for the treatment of castration-resistant prostate cancer [2,3] (CRPC), a serious cancer that afflicts men [4]. The oral capsule of Enzalutamide [5] was approved by the FDA for sale in August 2012. According to the statistics of the American Cancer Society [6], 217,730 new patients were diagnosed with prostate cancer by hospitals and clinics in the United States of America in 2010. Of these, 32,050 patients died as a result of prostate cancer within 2 years. Bicalutamide [7], flutamide [8] and abiraterone [9] were used to treat prostate cancer before the launch of enzalutamide. These drugs controlled CRPC effectively in only a small proportion of patients and caused some obvious side effects [10], such as hypertension, atrial fibrillation and hypokalemia. The cancer became resistant to these treatments in many patients after a period of about 2 years [11–13]. The development of enzalutamide provided a better choice for the treatment of CRPC, achieving sales of up to 1 billion dollars in 2013 and even better returns after that year. Research into new processes to produce the active pharmaceutical ingredient (API) enzalutamide is important and meaningful to continue delivery of this important drug.

Three main routes for the synthesis of enzalutamide have been reported. The first was undertaken by Sawyers et al. [14] in 2006. One obvious deficiency on this route is the very low yield of the last step, which would make producing the API costly at industrial scale. Song et al. [15] made a small improvement to this route using ethyl 2-bromobutyrate in place of 2-cyano-2-propanol, but this route remained unattractive for the production of **1**. Five years later, Thompson and co-workers [16] provided an alternative route to synthesize **1**, which improves on the original synthesis by removing the oxidation and reduction reactions. However, the yields of the last two steps are too low for economical kilo scale production of the API. Scientists from Medivation Inc. [17] also improved the second route and published their results in 2012. This synthesis overcame the poor yields of the final steps in the first and second routes, which justifies the use of high toxic iodomethane at a late stage of the synthesis and makes the third route more reasonable than the procedures of the first and second routes for commercial manufacture, but the crude product of which also need to be recrystallized for 2–3 times by isopropanol to get qualified API. A new route is needed for the efficient synthesis of **1** using moderate and environmentally friendly conditions and reagents. Herein we report a new five-step route to **1** that avoids highly toxic reagents and multiple recrystallization processes.

2. Results and discussion

Our new route [18,19] began with 4-bromo-2-fluoro-benzonic acid (**2a**) (Scheme 1). 5 g of **2a** were subjected to a methyl

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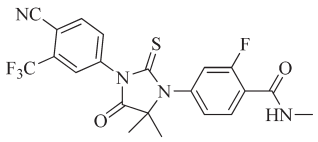
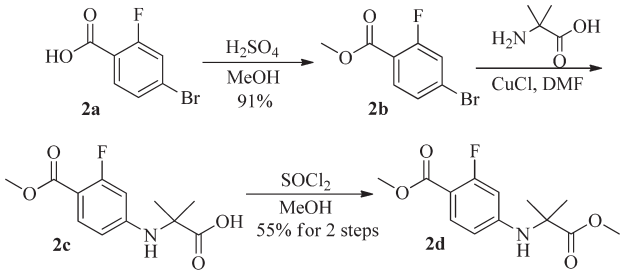
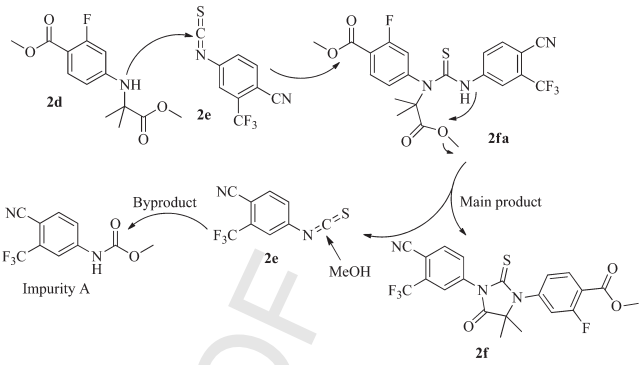


Fig. 1. Structure of enzalutaminde **1**.



Scheme 1. The first three steps of the new route to enzalutamide.



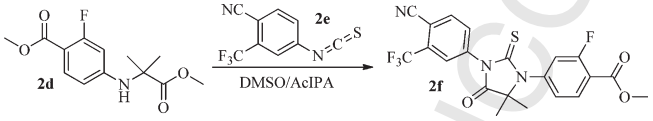
Scheme 2. Possible reaction mechanism of the fourth step on the new route.

esterification reaction catalyzed by sulfuric acid in methanol under reflux in the first step [20] to obtain methyl 4-bromo-2-fluoro-benzoate (**2b**) in 95% yield, which was easily isolated as a white solid by pouring the reaction solution into ice water after 24 h. The second step was an Ullmann reaction [21–23] for the ligation of **2b** with 2-amino-2-methylpropionic acid to give compound **2c**, which was reacted with thionyl chloride in refluxing methanol to obtain 3603 g of intermediate 2-fluoro-4-[(2-methoxy-1,1-dimethyl-2-oxoethyl)amino]-methyl ester (**2d**) in a total yield of 51% for the first three steps.

Intermediate **2d** was reacted with **2e** [24,25] in the fourth step of our new route. The reaction conditions for this step were optimized by the following steps (Table 1). The initial conditions used 1.0 mol of compounds **2d** and **2e** in a solution of dimethyl sulfoxide (DMSO) and isopropyl acetate at 95 °C to give only 30% of the desired product (Table 1, entry 1). Increasing the stoichiometry of compound **2e** resulted in higher yields (Table 1, entries 2–4). The final ratio of reactant **2e** was fixed at two equivalents relative to **2d** to ensure a cost-effective process. Lowering the reaction temperature to 80 °C dropped the yield to 57% (Table 1, entry 5). Ethyl acetate has similar properties to isopropyl acetate but was not suitable to achieve high yields because the lower boiling point of this solvent prevented an adequate reaction temperature (Table 1, entry 6). DMF was investigated as an alternative to DMSO but only a trace amount of the solid was crystalized from the mother solution, that is probably because DMSO is a highly polar solvent which is easier to be removed completely by water washing than that of DMF (Table 1, entry 7). We increased the reaction scale to over 1 kg and lowered the ratio of DMSO from 33% to 16% of the total solvent to obtain a 82% yield of the product after a 24-h reaction (Table 1, entry 8). Extending the reaction time to 36 or 48 h decreased the yields of the product by 5% and 12%, respectively (Table 1, entries 9 and 10).

Although the intermediate **2f** was successfully synthesized in 82% using the optimized conditions, it was unclear why the reaction required two equivalents of **2e**. A likely mechanism to explain this phenomenon is shown in Scheme 2. The lone pair electrons on the nitrogen atom of compound **2d** attack the most positively charged carbon on the isothiocyanate group of compound **2e** in the first step to form an active intermediate **2fa**. An intramolecular ring closing reaction of **2fa**, using the lone pair electrons of the nitrogen atom on the thiourea group to attack the methyl ester group, forms the stable five-member ring of the main product **2f**. A molecule of methanol is released by this process, which is a strong nucleophile and reacts with another molecule of compound **2e** to form methyl *N*-(3-trifluoromethyl-4-cayno-)-phenylcarbonate (impurity A) as a side product. Fortunately, impurity A was easily to be removed by recrystallization with isopropanol to get qualified **2f**. This possible mechanism explains why two molecules of reactant **2e** were consumed to form product **2f** and one molecule of side product impurity A.

Table 1
Optimization of the fourth step of the new route to enzalutamide.



Entry	**2d**:**2e** (molar ratio)[a]	Solvents (v/v)[b]	Temp. (°C)	Time (h)	Yield (%)[c]
1	1:1	DMSO:AcIPA = 1:2	95	24	30
2	1:1.5	DMSO:AcIPA = 1:2	95	24	45
3	1:2	DMSO:AcIPA = 1:2	95	24	65
4	1:3	DMSO:AcIPA = 1:2	95	24	68
5	1:2	DMSO:AcIPA = 1:2	80	24	57
6	1:2	DMSO:AcOEt = 1:2	65	24	45
7	1:2	DMF:AcIPA = 1:2	95	24	Trace
8	1:2	DMSO:AcIPA = 1:5	95	24	82
9	1:2	DMSO:AcIPA = 1:5	95	36	77
10	1:2	DMSO:AcIPA = 1:5	95	48	70

[a] For entries 1–7 the amount of **2d** was 269 g (1.0 mol) and for entries 8–10, the amount of **2d** was increased to 1200 g (4.46 mol).
[b] For entries 1–7, the total solvent volume was 810 mL and for entries 8–10 the total solvents volume was 3600 mL.
[c] Isolated yields.

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