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RAPID COMMUNICATION

A new synthesis of tafamidis *via* zinc-MsOH mediated reductive cyclisation strategy

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Abstract. A practical zinc-MsOH mediated intra-molecular reductive cyclisation and its application in the synthesis of tafamidis is presented starting from the readily available 3-hydroxy-4-nitrobenzoic acid as a precursor. The key reductive cyclization step involves the use of a combination of the readily available zinc and MsOH as the catalyst system. This methodology provides an attractive route to 2-aryl benzoxazoles from *ortho*-nitro phenols under mild reaction conditions. This methodology is developed on a multi-gram scale and without the need for column chromatography.

Keywords. Tafamidis; synthesis; reductive Cyclisation; zinc-MsOH; 2-aryl benzoxazoles.

1. Introduction

Transthyretin familial amyloid polyneuropathies (TTR-FAP) are a rare form of autosomal-dominant amyloidosis fibres resulting from TTR misfolding. This pathology induces nerve lesions and polyneuropathy, particularly in the peripheral nervous system. The onset of FAP occurs between 30 to 50 years of age and leads to death within ten years after diagnosis. Tafamidis (Figure 1) is discovered and developed by Scripps Research Centre in association with Pfizer in the treatment of FAP. Tafamidis lacks the anti-inflammatory activity contraindicated for patients with cardiomyopathy.[1] Recently, USFDA approved Tafamidis for the treatment of heart disease (cardiomyopathy) which is caused by transthyretin-mediated amyloidosis (ATTR-CM) in adults. ATTR is caused by a build-up of abnormal deposits of specific proteins known as amyloid in the body's organs and tissues. Tafamidis is the first FDA-approved treatments for ATTR-CM. Tafamidis and Tafamidis Meglumine are sold in the USA under the brand names 'Vyndamax' and 'Vyndaqel', respectively.[2]

Prior to our synthesis, very few synthetic procedures were documented in the literature for the synthesis of Tafamidis (**1**).[3–7] However, Tafamidis or 2-(3,5-dichlorophenyl)-6-benzoxazolecarboxylic acid is a structural analogue of 2-aryl benzoxazole. The most common approaches reported for the synthesis of 2-aryl benzoxazoles such as coupling of 2-aminophenols with carboxylic acid derivatives, the reaction of 2-aminophenols with an aldehyde by oxidative cyclization of imine intermediates, metal-catalyzed oxidative intramolecular C-O coupling of 2-haloanilides and metal-catalyzed direct C-H arylation reaction. However, these synthetic routes often utilized harsh reaction conditions including the use of strong acids or oxidants and high reaction temperature.[8a–9] Therefore, the development of alternative routes to benzoxazole ring formation is an imperative goal, because it would allow the use of mild reaction conditions and it would also prevail the requirement for using 2-aminophenols as precursors. Comparing with those intermolecular or intramolecular coupling methodologies, reductive cyclization of *ortho*-nitro phenols also provides an attractive route to benzoxazole ring formation. Unfortunately, only a few synthetic methods have been reported for reductive cyclization of *ortho*-nitro phenols to produce 2-substituted benzoxazoles.[8]

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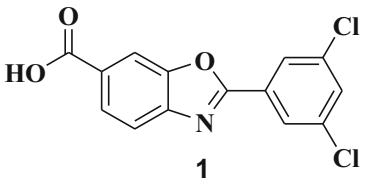


Figure 1. Chemical structure of Tafamidis (**1**).

Considering the restricted availability of starting materials (eg: 4-amino-3-hydroxybenzoic acid), we mainly evaluated alternative synthetic approaches from the commercially accessible starting materials. Herein, we report an attractive and alternative method for the synthesis of Tafamidis from commercially accessible inexpensive 4-hydroxy-3-nitrobenzoic acid *via* reductive cyclisation reaction. Success for this strategy would provide an alternative synthetic method for 2-aryl benzoxazoles from *ortho*-nitro phenols in mild conditions.

2. Experimental

Zinc dust was purchased from Merck Co Limited. Remaining all the chemicals were purchased from commercial sources and used without purification. ^{1}H and ^{13}C NMR spectra were recorded by a Bruker Avance 300 MHz and Varian 500 MHz spectrometer using TMS as internal standard in DMSO-d_6. The ^{1}H chemical shift values were reported in the δ scale relative to TMS (δ 0.00) and the ^{13}C chemical shift values were given relative to DMSO-d_6 as internal standards. High-resolution mass spectral (HRMS) analysis was performed using the electrospray ionization (ESI) method and a Xevo G2 QTOF mass spectrometer.

2.1 *Preparation of 3-(3,5-dichlorobenzoyloxy)-4-nitrobenzoic acid (7)*

To a stirred 20–30 °C suspension of 3-hydroxy-4-nitrobenzoic acid (**6**) (25 g, 0.136 mol) in a mixture of H_2O (500 mL) and isopropanol (250 mL), K_2CO_3 (47.1 g, 0.341 mol) was added in portions for about 30 min. The slurry was cooled to 0–10 °C and slowly added 3,5-dichlorobenzoyl chloride (**3**) (28.6 g, 0.136 mol) for about 30 min. The reaction mass was stirred for 2 h at 0–10 °C and 20–30 °C for 2 h. Then, the reaction mass was acidified with aqueous HCl solution. The aqueous layer was extracted with EtOAc (2 × 250 mL). Combined the organic extract and washed with H_2O (125 mL). The organic layer was concentrated under reduced pressure to afford pale yellow solid. To this solid, EtOH (650 mL) was added and warmed to reflux. The resultant solution was cooled and stirred for 1 h at 20–30 °C. The precipitated product was collected by filtration, dried and characterized as **7** as a pale yellow solid (37 g, 77%). ^{1}H NMR (300 MHz, DMSO-d_6): 8.08–8.13 (m, 4H), 8.20–8.21 (d, 1H, *J*=1.5 Hz), 8.31 (s, 1H), 8.33 (s, 1H), 13.88 (s, 1H); ^{13}C NMR (300 MHz, DMSO-d_6): 126.14, 126.28, 128.16, 128.50, 131.23, 133.88, 134.92, 136.85, 142.76, 143.69; HRMS Calculated for $C_{14}H_6Cl_2NO_6$ [$(M - H)^+$]: 353.9572, found: 353.9574.

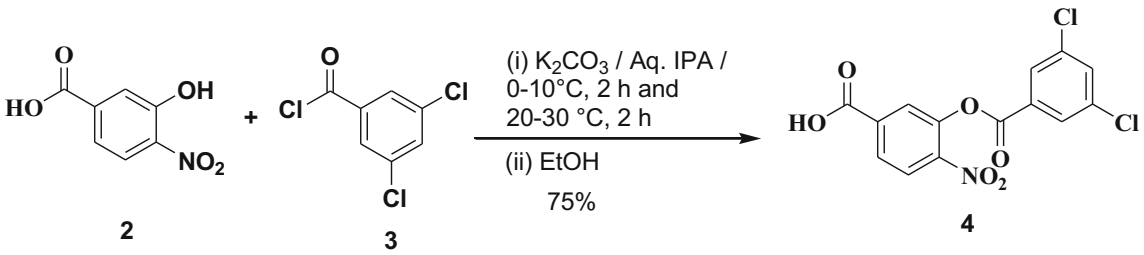
2.2 *Preparation of Tafamidis (1)*

To a stirred 20–30 °C suspension of 3-(3,5-dichlorobenzoyloxy)-4-nitrobenzoic acid (**7**) (5 g, 0.01 mol) in MsOH (75 mL), zinc dust (4.56 g, 0.07 mol) was added lot wise for 1 h. The slurry was warmed and stirred at 100–110 °C for 2 h. The slurry was cooled to ambient temperature, quenched to ice-water (750 mL) and stirred for 1 h at 0–5 °C. The precipitated product was collected by filtration and washed with water (2×10 mL). The wet product was suspended in isopropanol (50 mL) and warmed to reflux. The resultant slurry was stirred for 1 h at reflux and 1 h at 20–30 °C. The product was collected by filtration and dried to afford **1** as an off-white powder (2.5 g, 58%). ^{1}H NMR (300 MHz, DMSO-d_6): 7.83–7.86 (m, 2H), 7.97–7.69 (d, 1H, *J*=1.5 Hz), 8.00–7.99 (d, 1H, *J*=1.5 Hz), 8.04–8.03 (d, 1H, *J*=1.8 Hz), 8.20–8.19 (m, 1H), 13.25 (s, 1H); HRMS Calculated for $C_{14}H_6Cl_2NO_3$ [$(M - H)^+$]: 305.9725, found: 305.9734.

3. Results and Discussion

Our present synthesis of Tafamidis was started from a new precursor 3-(3,5-dichlorobenzoyloxy)-4-nitrobenzoic acid (**4**). A one-step *O*-benzoylation reaction between 3-hydroxy-4-nitrobenzoic acid (**2**) and 3,5-dichlorobenzoyl chloride (**3**) in the presence of inexpensive base K_2CO_3, in aqueous isopropanol at temperatures 0–10 °C for 2 h and 20–30 °C for 2 h, produced 3-(3,5-dichlorobenzoyloxy)-4-nitrobenzoic acid (**4**) in 75% yield as shown in Scheme 1.

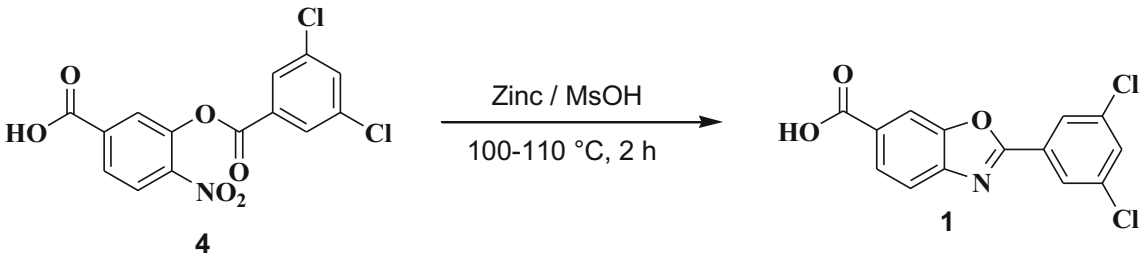
Subsequently, we evaluated the suitable catalyst system for the reductive cyclisation reaction. Zinc metal is a commercially accessible inexpensive reductant in synthetically useful organic transformations. In the course of studying the utility of zinc metal for efficient reductive organic transformations, we found that various heterocyclic compounds *via* inter- or intramolecular reduction-triggered one-pot



Scheme 1. Synthesis of 3-(3,5-dichlorobenzoyloxy)-4-nitrobenzoic acid (**4**) from 3-hydroxy-4-nitrobenzoic acid (**2**).

Table 1. Screening reaction conditions.

Entry	Conditions	Product	
		Major	Trace
1	Zn (5 moles), AcOH (15 times), 60 °C, 16 h	**1a**	
2	Zn (5 moles), NH_4Cl (5 moles), MsOH(5 times), DMF, 90 °C, 4 h	**1a**	**1**
3	Zn (5 moles), MsOH (5 times), AcOH (5 times), 90 °C, 4 h	**1a**	**1**
4	Zn (5 moles), MsOH (5 times), AcOH(15 times), reflux, 2 h	**1a**	**1**
5	Zn (5 moles), MsOH(15 times), AcOH(5 times), *o*-xylene, reflux, 10 h	**1a**	**1**
6	Zn (5 moles), MsOH (5 times), *o*-xylene, reflux, 16 h	**1a**	**1**
7	Zn (5 moles), MsOH (15 times), *o*-xylene, reflux, 24 h	**1a**	**1**
8	Zn (5 moles), MsOH (15 times), 100–110 °C, 2 h	**1**	



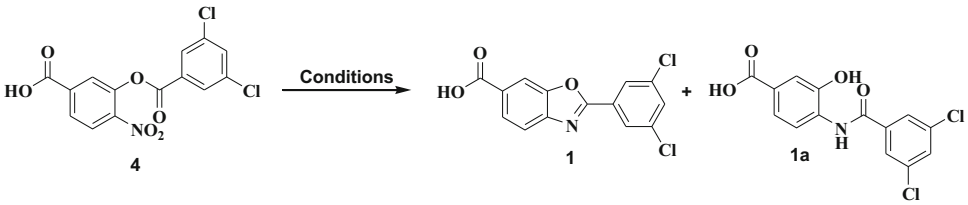
Scheme 2. Synthesis of Tafamidis (**1**) from 3-(3,5-dichlorobenzoyloxy)-4-nitrobenzoic acid (**4**).

reactions.[10] We realized that conceptually, similar conditions could also be applied to a facile synthesis of tafamidis starting from 3-(3,5-dichlorobenzoyloxy)-4-nitrobenzoic acid (**4**) by reductive cyclisation if appropriate reductive conditions were identified.

Our initial studies focused on reductive cyclisation of 3-(3,5-dichlorobenzoyloxy)-4-nitrobenzoic acid (**4**) to produce tafamidis. A reagent combination of zinc in AcOH (Table 1, entry 1) at 60 °C produced 3-(3,5-dichlorobenzoyloxy)-4-aminobenzoic acid (**1a**), a key amide intermediate[3,4] of Tafamidis.

Based on this experimental result, we implicated the significance of temperature in this reductive cyclisation reaction and opted to perform the reactions at high temperatures. Reductive cyclisation in the presence of zinc-NH_4Cl in a mixture of MsOH and DMF at 90 °C for 4 h also produced majorly **1a** (Table 1, entry 2). A similar result was obtained by heating 4-(3,5-dichlorobenzamido)-3-hydroxybenzoic acid (**4**) in the presence of zinc in a mixture of MsOH and AcOH at 90 °C (Table 1, entry 3). Consequently, a set of experiments were carried out in *o*-xylene at reflux

condition for longer hours produced trace level of tafamidis as summarized in Table 1 (entry 4 to entry 7).



To our delight, 4-(3,5-dichlorobenzamido)-3-hydroxybenzoic acid (**4**) was cyclised smoothly in the presence of zinc in MsOH at 100–110 °C temperature within 2 h and produced tafamidis (Table 1, entry 8) as shown in Scheme 2. Upon completion of the reaction, as monitored by TLC, the mixture was quenched to ice-cooled water. The precipitated product was collected and purified in isopropanol to afford pure tafamidis in 58% yield.

4. Conclusions

In summary, a practical and straightforward approach towards the synthesis of tafamidis *via* zinc-MsOH reductive cyclisation reaction was reported. This methodology is useful for the preparation of 2-aryl benzoxazoles from *ortho*-nitro phenols. The key reductive cyclization step involves the use of inexpensive and easy-to-handle zinc in combination with MsOH under mild conditions. The use of a simple zinc-MsOH as catalyst renders the protocol suitable for large-scale synthesis, providing a valuable synthetic tool for industrial applications.

Supplementary Information (SI)

^{1}H NMR and ^{13}C NMR data is available at www.ias.ac.in/chemsci.

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Conflict of interest The authors declare no conflict of interest.

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