An Easy Access to 7-Methyl-2-naphthalenecarbonitrile

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A practical and cost-effective procedure has been developed for the synthesis of 7-methyl-2-naphthalenecarbonitrile, the precursor of the anticoagulant agents YM-60828 or YM-96765. This new route generates the key intermediate in only two steps from readily available 3-cyanopropionaldehyde dimethyl acetal and *m*-tolualdehyde, without requiring chromatographic purification. The synthesis involves condensation of the cyano derivative with the aldehyde and subsequent cyclodehydration.

Key words inhibitor; bicyclic compound; nitrile; condensation; cyclization

Thromboembolic diseases continue to be a leading cause of morbidity and mortality in the developed world, and the use of anticoagulant drugs is a primary clinical strategy to treat and prevent these diseases. Factor Xa inhibitors have the potential to be superior anticoagulant agents, and thus the search for novel factor Xa inhibitors has emerged as one of the most active areas of current drug discovery.

Several potent factor Xa inhibitors containing naphthylamidine moieties have been reported,[1—5] and representative structures of these inhibitors are shown in Fig. 1. These drugs have a common precursor, 7-methyl-2-naphthalenecarbonitrile (**1**), and several methods have been reported for preparation of this compound.[6—10] Earlier syntheses of compound **1** are multi-step procedures[6,8] or require high temperature (flame-heating or heating to 400 °C),[7,9] and hence they are impractical and unsuitable for commercial exploitation. More recently, Yokoyama *et al.* have described the preparation of compound **1** in four steps, in which 2,7-dimethylnaphthalene was used as the starting material.[10] However, 2,7-dimethylnaphthalene is not readily available from commercial sources, and this method also involves a selective transformation of a symmetrical starting material to an asymmetrical target compound. These two problems contribute to decreased synthetic efficacy. Due to the high worldwide market value of factor Xa inhibitors, development of an effective synthetic procedure for the synthesis of the key precursor **1** remains as an important and challenging task. Herein, we present a practical and efficient synthesis of 7-methyl-2-naphthalenecarbonitrile (**1**) starting from two common, readily available starting materials: *m*-tolualdehyde (**2**) and 3-cyanopropionaldehyde dimethyl acetal (**3**).

Teague *et al.* have reported that condensation of a 3-cyanopropionaldehyde dialkyl acetal with a methoxy-activated aromatic aldehyde, followed by treatment with sulfuric acid, yields a substituted naphthalene product.[11] Although this method is limited to activated benzaldehydes such as methoxybenzaldehyde, we adapted it for our target compound using a weakly activated benzaldehyde, *m*-tolualdehyde (Chart 1). Condensation of **2** with **3** in the presence of LDA (lithium diisopropylamide) gave intermediate alcohol **4**, and the crude alcohol was then refluxed in 20% aqueous sulfuric acid to afford compound **1** in 43% yield after chromatographic purification (Chart 1, Entry 1). The more hindered cyclization product, 5-methyl-2-naphthalenecarbonitrile, was not observed.

Several different reaction conditions were used in optimizing the reaction for multi-gram preparations, and the results are summarized in Chart 1. Sodium amide,[12] *n*-butyllithium,[13—15] a combination of di-*n*-butylboryl triflate and diisopropylamine,[16] potassium *t*-butoxide,[17] and a combination of proazaphosphatrane and magnesium sulfate[18] have been used as condensation reagents for acetonitrile with benzaldehyde. Our attention was drawn to the reaction in the presence of potassium *t*-butoxide, since it has the following advantages: (1) potassium *t*-butoxide is readily available from commercial sources, and (2) it does not cause evolution of gas from the reaction mixture. However, condensation of **3** with **2** in the presence of potassium *t*-butoxide followed by cyclization in 20% aqueous sulfuric acid gave compound **1** with an overall yield of 34% (Chart 1, Entry 2); hence, the application of potassium *t*-butoxide as a base resulted in a disappointingly low yield. In contrast, use of Bradsher's reagent as a cyclodehydration agent[19] gave good results. Cyclization of the crude coupling product **4** with aqueous hydrobromic acid in acetic acid afforded the target compound **1** with an overall yield of 66% (Chart 1, Entry 3). Moreover, the crystalline naphthalene derivative **1** precipitated from the resulting reaction mixture, and simple filtration allowed iso-

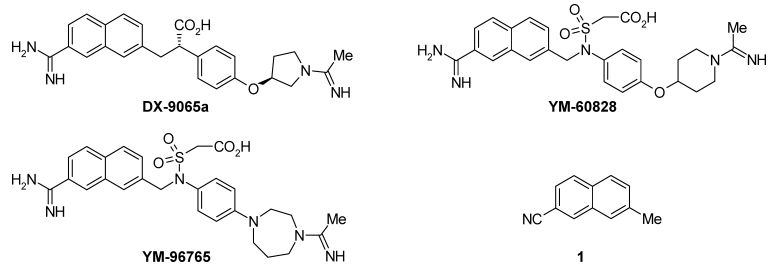

Fig. 1. Representative Structures of Factor Xa Inhibitors and Their Precursor **1**

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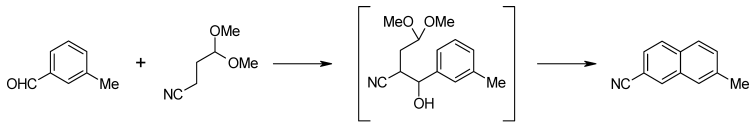

2 3 4 1

Entry	Condition		Yield (%)
	Condensation process	Cyclodehydration process	
1	LDA, THF, −78 °C to r.t.	20% sulfuric acid, 100 °C	43[a]
2	KO*t*-Bu, THF, −78 °C to r.t.	20% sulfuric acid, 100 °C	34[a]
3	LDA, THF, −78 °C to r.t.	48% hydrobromic acid, AcOH, 100 °C	66[a]
4	LDA, THF, −78 °C to r.t.	48% hydrobromic acid, AcOH, 100 °C	49[b]

a) Yield after chromatographic purification. *b*) Isolated by filtration of the reaction mixture.

Chart 1. Synthesis of 7-Methyl-2-naphtalenecarbonitrile (**1**)

lation of the pure target compound (Chart 1, Entry 4). These conditions abridged the work-up procedures of the reaction and furnished compound **1** with excellent reproducibility, which led us to conclude that this procedure is practical for multi-gram preparation. We subsequently confirmed that the method is applicable for scale-up to as much as 63 g of compound **1**.

In conclusion, we have successfully established a simple, practical, and cost-effective synthesis of 7-methyl-2-naphthalenecarbonitrile. The key features of this procedure are (1) an efficient condensation of 3-cyanopropionaldehyde dimethyl acetal with *m*-tolualdehyde; and (2) reliable cyclodehydration of the intermediate alcohol. This method will be useful for synthesis of naphthalene derivatives from weakly activated benzaldehydes such as *m*-tolualdehyde, compared with strongly activated benzaldehydes such as methoxybenzaldehyde derivatives. The final target compound can be isolated without chromatographic purification, and we anticipate that this new and straightforward procedure will be of great utility in the preparation and production of anticoagulant agents.

Experimental

Melting points were determined using a Yanaco MP-500D melting point apparatus, and are uncorrected. IR absorption spectra were obtained using a Horiba FT-720 spectrometer. ^{1}H-NMR spectra were recorded on a JEOL EX400 spectrometer (400 MHz). ^{13}C-NMR spectra were recorded on a JEOL EX400 spectrometer (100 MHz). The chemical shifts (δ) are expressed in ppm relative to tetramethylsilane, and spectra were recorded in DMSO-d_6. MS spectra were recorded on a Fisons TRIO1000 spectrometer using electron impact ionization at 70 eV. Elemental analysis was performed with a Yanaco MT-5 microanalyzer (C, H and N). Analytical thin-layer chromatography (TLC) were performed on a glass plates precoated with silica gel (Merck Silica gel 60 F_{254}). Visualization was accomplished by UV light (254 nm) and iodine vapor. 3-Cyanopropionaldehyde dimethyl acetal and *m*-tolualdehyde were purchased from Tokyo Kasei Kogyo Co., Ltd. and were used without further purification. A solution of lithium diisopropylamide in cyclohexane was purchased from Aldrich Chemical Co. All solvents employed in these experiments were reagent grade obtained from Kanto Chemical Co. and were used without further purification.

7-Methyl-2-naphthalenecarbonitrile (1) In a three-necked round bottom flask equipped with stirrer, a solution of lithium diisopropylamide (1.5 M in cyclohexane; 616 ml, 924 mmol) and tetrahydrofuran (740 ml) was taken and cooled to −78 °C under argon. To the mixture was added dropwise 3-cyanopropionaldehyde dimethyl acetal (**3**) (105 ml, 806 mmol) and the whole was stirred for 1 h. To the reaction mixture *m*-tolualdehyde (**2**) (90.0 ml, 763 mmol) was added dropwise at −78 °C. The whole was stirred for 0.5 h, and allowed to warm to ambient temperature and then stirred for a further 2 h. After addition of H_2O (500 ml) at 0 °C, the reaction mixture was extracted with ethyl acetate (300 ml). The extract was washed with H_2O and then brine, dried over magnesium sulfate, and concentrated *in vacuo* to yield a pale yellow oil (191.74 g). A mixture of the resulting oil (191.74 g), glacial AcOH (769 ml), and hydrobromic acid (48 wt% in water; 601 ml) was stirred at 100 °C for 2 h. The reaction mixture was cooled to ambient temperature and the resulting precipitate was filtered. The collected solid was washed with a mixture of glacial AcOH and H_2O (1 : 1 by volume) and then H_2O, and dried at 40 °C under reduced pressure to yield the title compound as a beige solid.

Yield: 63.2 g (49%); mp 136—137 °C (lit.[10] mp 132.4—133.3 °C). IR (KBr): 2227, 916, 848 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.51 (s, 3H, CH_3), 7.56 (d, 1H, J=8.0 Hz, H-6), 7.70 (d, 1H, J=8.4 Hz, H-4), 7.79 (s, 1H, H-8), 7.94 (d, 1H, J=8.0 Hz, H-5), 8.04 (d, 1H, J=8.4 Hz, H-3), 8.42 (s, 1H, H-1). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 21.16, 108.34, 119.22, 125.39, 127.06, 127.76, 128.97, 131.37, 132.03, 132.54, 133.48, 137.27. EI-MS: m/z=167 $[M]^+$. *Anal.* Calcd for $C_{12}H_9N$: C, 86.20; H, 5.43; N, 8.38. Found: C, 86.17; H, 5.47; N, 8.34.

The analysis of the first condensation product by TLC on silica gel (*n*-hexane–ethyl acetate, 2 : 1) gave the following results; a spot, which was weakly UV-active, was detected upon exposure to iodine vapor at an *Rf* value of 0.23. The analysis of the title compound by TLC on silica gel (*n*-hexane–ethyl acetate, 8 : 1) gave the following results; a spot, which was strongly UV-active, was detected upon exposure to iodine vapor at an *Rf* value of 0.38.

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