Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 61 (2005) 2683–2688

Synthesis of 2-mesityl-3-methylpyrrole via the Trofimov reaction for a new BODIPY with hindered internal rotation

Alexey B. Zaitsev,[a] Rachel Méallet-Renault,[b] Elena Yu. Schmidt,[a] Al'bina I. Mikhaleva,[a,*] Sophie Badré,[b] Cécile Dumas,[b] Alexander M. Vasil'tsov,[a] Nadezhda V. Zorina[a] and Robert B. Pansu[b]

[a]*A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 1 Favorsky Str., Irkutsk 664033, Russian Federation*
[b]*Laboratoire de Photophysique et Photochimie Supramoléculaires et Macromoléculaires (CNRS UMR 8531), Ecole Normale Supérieure de Cachan, 61 Avenue du Président Wilson, 94235 Cachan cedex, France*

Received 2 September 2004; revised 21 December 2004; accepted 13 January 2005

Abstract—The reaction of *E*-ethylmesitylketoxime with acetylene in the system KOH/DMSO (the Trofimov reaction) (70–74 °C, 3 h, atmosphere pressure) affords 2-mesityl-3-methylpyrrole (23%), 2-mesityl-3-methyl-1-vinylpyrrole (8%), *Z*- (5%) and *E*- (2%) isomers of *O*-vinylethylmesitylketoxime. Initial ethylmesitylketoxime was prepared in two ways: via very slow oximation of ethylmesitylketone in 30% yield after 8 months, and, more efficiently, by oximation of ethylmesitylketimine hydrochloride derived from bromomesitylene in several steps. 2-Mesityl-3-methylpyrrole was used for the synthesis of 4,4-difluoro-2,6-dimethyl-3,5,8-trimesityl-4-bora-3a,4a-diaza-*s*-indacene with mesityl substituents having hindered internal rotation and preventing π-stacking at high concentrations. The latter factor enables the fluorescence of crystals of the prepared BODIPY, a feature that was not previously documented for such molecules.

1. Introduction

For more than 30 years since their discovery[1] BODIPY (4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene) derivatives have enjoyed wide popularity among experts in chemistry,[2] physics,[3] biology[4] and related fields[5] for their exceptional optical properties.

During the practical realization of various devices based on BODIPY dyes, when high concentrations are needed, intermolecular π-stacking can cancel out their advantages such as high fluorescence quantum yields and intensities.[6] To the best of our knowledge, so far, no fluorescent crystals of BODIPY have been reported, although the pigments (solid dyes) based on them, due to their anticipated high brightness and enhanced resistance to photobleaching, might find extensive application. Therefore, the design of new boradiazaindacenes with hindered π-stacking, which is considered as the principal culprit behind the loss of fluorescence in crystalline form, has remained a challenge.

Herein, we describe a synthesis of the first representatives of boradiazaindacenes, which are fluorescent in a crystalline form. The main idea was to develop an approach to structures with bulky mesityl substituents attached to the BODIPY core, distorting overall planarity and thus hampering the π-stacking at high concentrations. Furthermore, the hindered internal rotation of mesityl rings reduces non-radiative relaxation of excited states, hence decreasing fluorescence quantum yields.[7]

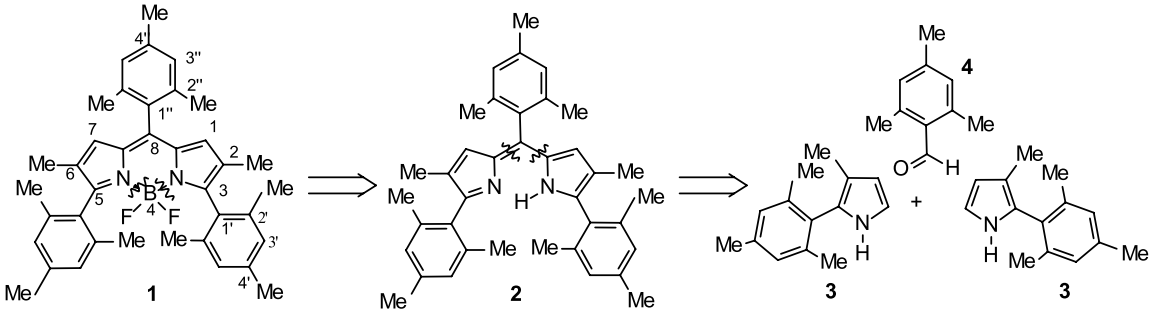
2. Results and discussion

As a synthetic target 4,4-difluoro-2,6-dimethyl-3,5,8-trimesityl-4-bora-3a,4a-diaza-*s*-indacene **1** was chosen because its 2,6-methyl groups could additionally hinder internal rotation and force benzene rings out of the molecular plane more efficiently.

The disconnection of **1** (reverse to the synthesis of BODIPY via the reaction of boron trifluoride etherate with dipyrromethenes derived from pyrroles and aldehydes[8]) leads to dipyrromethene **2** and then to 2-mesityl-3-methylpyrrole **3** and 2,4,6-trimethylbenzaldehyde **4** (Scheme 1).

Keywords: 2-Mesitylpyrroles; Oximes; Acetylene; Superbases; BODIPY; Hindered internal rotation; Fluorophores; π-Stacking.
* Corresponding author. Tel.: +7 3952 42 24 09/42 58 71; fax: +7 3952 41 93 46; e-mail: mikh@irioch.irk.ru

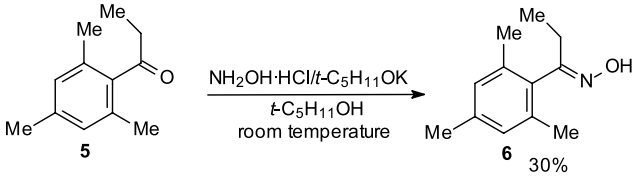
0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.01.065



Scheme 1.

To accomplish this synthetic sequence, we had to develop an approach to pyrrole **3**. The Trofimov reaction (reaction of ketoximes with acetylene in superbasic media affording pyrroles and *N*-vinyl pyrroles)[9,10] might be useful for approaching **3** from ethylmesitylketoxime **6**. However, until the present work there were no examples of a successful application of this reaction to highly hindered ketoximes and this exploration could shed light on whether such ketoximes are capable of affording pyrroles upon reaction with acetylene.

Meanwhile, at the very beginning of the study we encountered a serious problem of very low reactivity of ethylmesitylketone **5** towards hydroxylamine. Oximation by refluxing mixtures of ketones and hydroxylamine hydrochloride in pyridine, effective in the synthesis of some hindered oximes,[11] proved to be inefficient in the case of **5** (even when microwave activation was applied) and yielded only trace amounts of **6**. The 'lethargic' oximation, although it gave mesitylmethylketoxime from mesitylmethylketone in 98% yield in 28 days,[12] after application to **5** afforded its oxime **6** (mostly *E*-isomer) only in 30% yield after 8 months (Scheme 2).



Scheme 2.

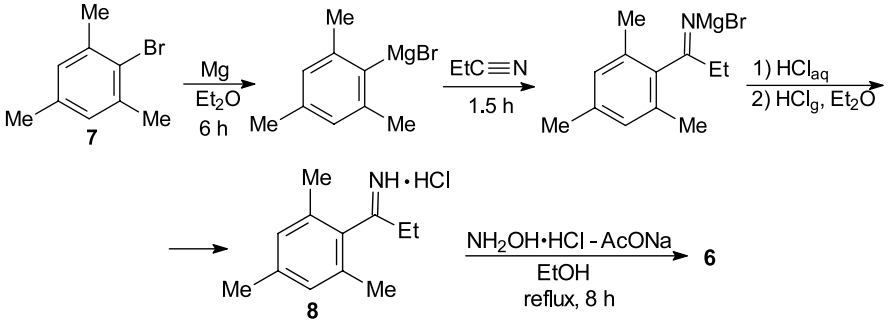
It is obvious that the mesityl group blocks the carbonyl carbon in ketone **5**, and the blockage becomes much more pronounced on passing from mesitylmethylketone to ethylmesitylketone **5**.

To develop a better access to the ketoxime **6** we, therefore, attempted the oximation of ethylmesitylimine hydrochloride **8** similar to that used previously for the synthesis of some other mesityl oximes.[13] This procedure, though multistep, allowed us to approach **6** from bromomesitylene **7** in 39% yield in a matter of 2 days (Scheme 3).

The reaction of the *E*-isomer of oxime **6** with acetylene in the KOH/DMSO superbasic system (70–74 °C, 3 h, atmospheric pressure) gave 2-mesityl-3-methylpyrrole **3** (23%), 2-mesityl-3-methyl-1-vinylpyrrole **9** (8%), *Z*- (5%) and *E*- (2%) isomers of *O*-vinylethylmesitylketoxime **10** (Scheme 4).

A short contact (70 °C, 5 min) of the *E*-isomer of **6** with acetylene in the KOH/DMSO system under increased acetylene pressure (initial pressure 17 atm) led to *O*-vinylketoxime **10** (23%) (*E*–*Z*∼1:2) and pyrrole **3** (12%) (^{1}H NMR).

Interestingly, the *E*-isomer of oxime **6** was transformed mainly to the *Z*-isomer of *O*-vinylketoxime **10**. This is a striking contrast to, for example, methylphenylketoxime, which under similar conditions gave only the *E*-isomer of *O*-vinylmethylphenylketoxime.[14] Heating of the *E*-isomer of the oxime **6** at 80 °C for 1 h in KOH/DMSO system resulted in the formation of 1:1 mixture of its *E*- and *Z*-isomers. Thus, the *E*–*Z* isomerization of **6** occurs under the reaction conditions, and steric hindrances imparted on the oxime hydroxyl by both mesityl and ethyl groups in **6** are similar. The specific behaviour of the oxime **6** can be rationalized assuming twisting of mesityl ring out of the C–C=N–O plane. When twisted, it strongly hinders the C=N (C=O) carbon (as evident from the difficulty of oximation of mesityl ketones) and, on the other hand, makes



Scheme 3.