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Mechanosynthesis of Solid-State Benzoxazoles for Use as OLED †

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Abstract

Mechanosynthesis in solid state represents an efficient method for synthesizing precursor molecules required for the development of organic light-emitting diode devices. In this study, nine benzoxazoles were synthesized using a high-energy planetary ball mill. A 2^k factorial experimental design was employed, focusing on reactor operating conditions. The mechanosynthesis process was confirmed by Nuclear Magnetic Resonance and Infrared spectrometry analyses, while Ultraviolet spectroscopy indicated the formation of luminescent products. Reactions were typically completed within 1 to 3 h, affording yields ranging from 19% to 98%.

Keywords: organic synthesis; mechanosynthesis; green chemistry; heterocycles

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1. Introduction

Mechanochemical approaches to organic synthesis, particularly mechanochemical multicomponent reactions, have been recognized by both academia and industry as powerful methodologies for developing green synthetic strategies. Their advantages include: (a) elimination or drastic reduction of bulk solvents; (b) accelerated reaction rates, higher conversions, and improved selectivities; (c) precise stoichiometry with minimal reagent excess; and (d) access to novel multicomponent transformations that are challenging, or even unattainable, under conventional solution-based conditions [1–11]. This latter advantage not only expands the library of accessible organic molecules but also stimulates the design of innovative reaction pathways. Furthermore, chemical structures with outstanding optical and electrical properties have been synthesized using mechanochemistry, with potential activity for use as electroluminescent materials in the production of organic light-emitting diodes (OLEDs) [12,13].

Benzoxazoles are significant scaffolds in organic synthesis because of their applications across molecular biology, pharmaceutical chemistry, biomedical engineering, and materials chemistry. In materials chemistry, they underpin the development of new electroluminescent and photoluminescent materials, as well as organic light emitting diodes [14–19]. Structural modifications at the 2-position and in the benzene ring of benzoxazole have yielded a variety of 2-benzoxazoles [15–17,20–24]. These compounds exhibit an

electronic push-pull effect through π-system delocalization, a highly desirable attribute in materials with optoelectronic properties. Given their significance, there is growing interest in developing innovative organic synthesis methodologies that produce these compounds more efficiently while adhering to the principles of Green Chemistry. In particular, strategies that minimize step count and maximize overall yield are sought. Mechanosynthesis and multicomponent reactions enable one-pot syntheses, a powerful approach to accessing complex compounds [20,21].

Herein, we present the mechanosynthesis of nine 2-arylbenzoxazoles through oxidative cyclization, previously forming an imine. We compare the yield and reaction time of this method with a traditional dissolution approach [20].

2. Materials and Methods

Reagents included salicylaldehyde, 5-bromo-2-hydroxybenzaldehyde, 2-hydroxy-5-nitrobenzaldehyde, 2-aminophenol, 3-methyl-2-aminophenol, and 4-methyl-2-aminophenol. Phenylboronic acid [$PhB(OH)_2$] and potassium cyanide (KCN) served as catalysts. Deuterated solvents for NMR were methanol-*d* (MeOD), chloroform-*d* (CDCl3), and dimethylsulfoxide-*d6* (DMSO-*d6*). Tetramethylsilane (TMS) was used as the internal reference. Reaction products were recrystallized from anhydrous methanol. All reagents and solvents were obtained from Sigma Aldrich.

Mechanosynthesis of 2-arylbenzoxazoles was carried out in a Premium Line planetary ball mill (Pulverisette 7, Idar-Oberstein, Germany). using a 45 mL reactor charged with ten 10 mm diameter balls. Each experiment was performed in triplicate. Thin-layer chromatography (TLC) was realized on Merck Silica Gel 60 F_{254} plates with hexane/ethyl acetate (80:20, *v*/*v*) as the mobile phase; spots were visualized under UV light at 254 and 365 nm. Melting points were measured on an EZ Melt AMPA instrument (Stanford Research Systems, Zaventem, Belgium) using open capillaries and are reported in degrees Celsius. Infrared spectra were recorded on a Spectrum 100 FTIR-ATR (Perkin Elmer, Waltham, MA, USA) over 4000–500 cm^{-1} at a scan rate of 4 scans per minute. ^{1}H and ^{13}C NMR spectra were acquired on a 400 MHz spectrometer (Varian, Palo Alto, CA, USA).

To evaluate the effects of reactor operating conditions, a 2^k factorial experiment design was implemented: rotational speed (10 Hz and 20 Hz) and the number of milling balls (5 and 10). Each treatment combination was conducted in triplicate.

3. Results and Discussion

A two-factor, two-level (2^2) factorial experiment design was used to optimize the milling parameters for benzoxazole formation. The optimal operating point was identified at the high level for both factors, rotational speed of 20 Hz and a charge of 10 milling balls, indicating that increased impact energy (rpm) and collision frequency (ball number) both contribute positively to reaction performance within the explored domain. Under these conditions, the mechanosynthesis delivered benzoxazoles **7–15** (Figure 1).

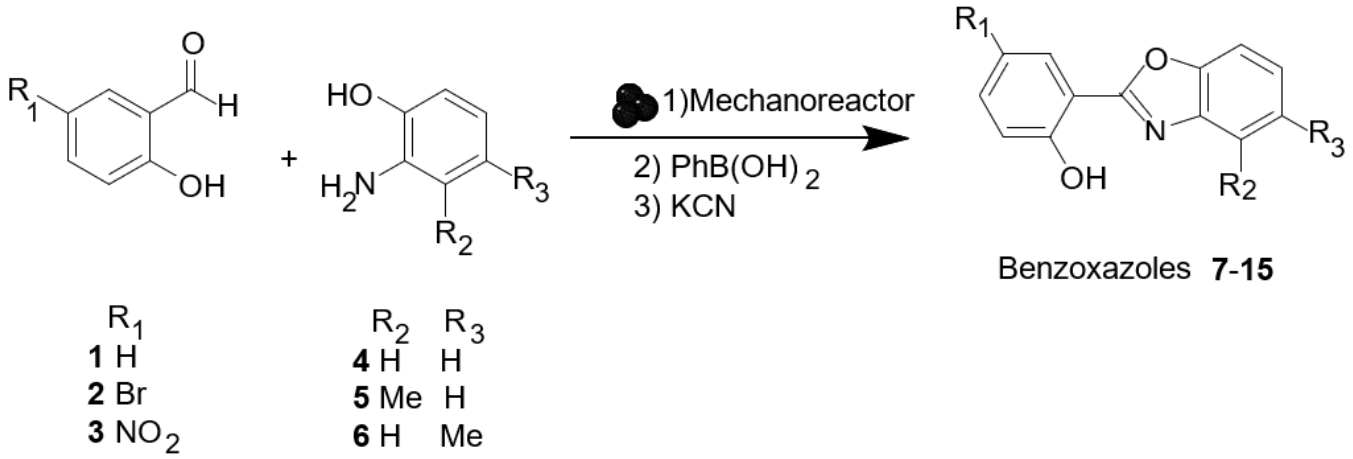

Figure 1. Mechanosynthesis of benzoxazoles **7–15** promoted by $PhB(OH)_2$ and KCN.

Notably, compounds **13–15**, which have been reported in the literature in very low yields [22], were obtained in substantially higher yields under our optimized mechanochemical protocol, underscoring the utility of solvent-minimized, high-energy milling for these substrates. Each crude product was recrystallized from MeOH to give microcrystalline solids and was characterized by FTIR-ATR and $^{1}H/^{13}C$ NMR spectroscopy. For structure confirmation of the nitro-substituted series, representative ^{1}H and $^{1}H–^{1}H$ COSY spectra of **13–15** are shown in Figure 2; the correlation patterns are consistent with the proposed substitution patterns on the benzoxazole framework.

Short milling times revealed accumulation of the corresponding imine intermediates, consistent with a stepwise process involving initial condensation of salicylaldehyde 1 with aminophenol 2 followed by oxidative cyclization. Under these abbreviated conditions, imines **16–24** were isolated in nearly quantitative yields (Table 1; Figure 3).

Table 1. Yields and reaction times for benzoxazoles **7–15** and imines **16–24** (mechanosynthesis).

Benzoxazole	Yield (%)	Reaction Time (min)	Imine	Yield (%)	Reaction Time (min)
7	56.15	70	**16**	91.22	2
8	25.12	70	**17**	96.35	2
9	52.45	70	**18**	88.19	2
10	53.03	70	**19**	88.85	2
11	24.41	180	**20**[1]	42.50	20
12	40.61	120	**21**	97.56	4
13	36.98	120	**22**	92.04	4
14	18.76	180	**23** [1]	34.12	20
15	24.30	120	**24**	89.31	4

[1] Compounds **20** and **23** are insoluble in MeOD, $CDCl_3$ and DMSO-*d*$_6$.

The imines intermediates were characterized by FTIR-ATR and NMR, except for **21** and **23**, which were insoluble in the deuterated solvents MeOD, $CDCl_3$, and DMSO-*d6* and were therefore assigned on the basis of FTIR-ATR data alone.

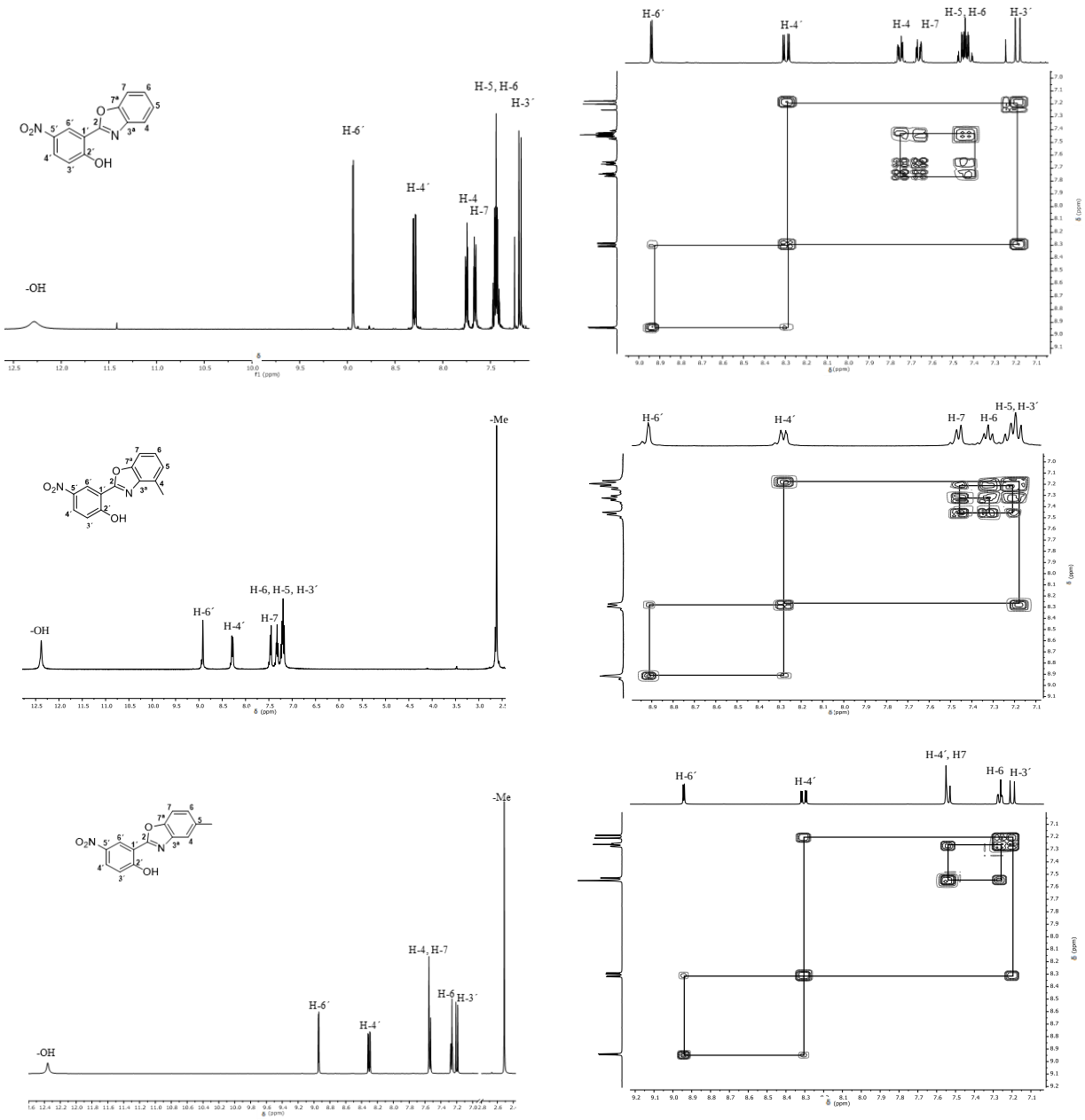

Figure 2. Structure confirmation of 13–15 by NMR in $CDCl_3$: (**a**) ^1H spectra; (**b**) ^1H–^1H COSY. Top: **13** (2-(5′-nitro-2′-hydroxyphenyl)benzoxazole); middle: **14** (2-(5′-nitro-2′-hydroxyphenyl)-4-methylbenzoxazole); bottom: **15** (2-(5′-nitro-2′-hydroxyphenyl)-5-methylbenzoxazole).

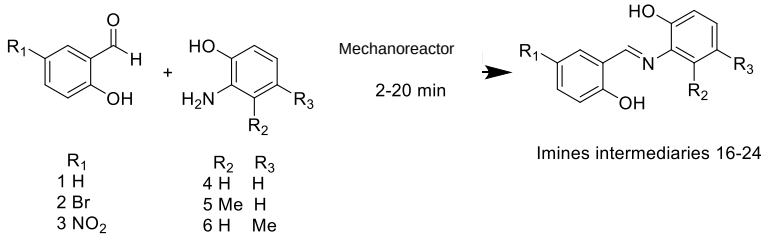

Figure 3. Summary of isolated imine intermediates **16–24** obtained at short milling times.

Collectively, these results demonstrate that optimizing mechanical energy input and collision frequency enables efficient access to benzoxazoles **7–15** and provides a

convenient handle to intercept and characterize imine intermediates **16–24**. The improved outcomes for **13–15** relative to solution-phase reports highlight the particular advantage of the mechanochemical protocol for substrates that are otherwise low-yielding.

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