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Proceeding Paper

BODIPY-4*H*-Pyran Hybrids Synthesis †

Alexis S. Zamora-Vázquez, Diana E. Ramirez-Ornelas, Enrique Alvarado-Martínez, Miguel A. Vázquez * and Eduardo Peña-Cabrera *

Departamento de Química, Universidad de Guanajuato, Noria Alta S/N, Guanajuato 36050, Mexico; as.zamoravazquez@ugto.mx (A.S.Z.-V.); ramirez.de@ugto.mx (D.E.R.-O.); e.alvaradomartinez@ugto.mx (E.A.-M.)

* Correspondence: mvazquez@ugto.mx (M.A.V.); eduardop@ugto.mx (E.P.-C.)

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Abstract

This contribution describes the novel synthesis of a series of fluorescent heterocycles obtained through one-pot multicomponent reactions (MCRs). Formyl-containing BODIPYs have been shown to efficiently participate in Ugi and Passerini reactions, affording fluorescent adducts. Likewise, 4H-pyrans can be synthesized via a base-catalyzed reaction involving an aldehyde, malononitrile, and ethyl acetoacetate. In this study, we investigated the role of formyl-containing BODIPY in MCRs for the preparation of 4H-pyran–BODIPY hybrids, achieving yields of 25–72% in 4–24 h. To further improve the process, ultrasound irradiation was applied, affording comparable yields (35–64%) with a significant decrease in reaction times (0.5–1.5 h).

Keywords: MCR; BODIPY; heterocycles; ultrasound irradiation

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1. Introduction

The development of efficient methodologies for rapidly constructing structurally complex molecules remains a central goal in synthetic chemistry. Multicomponent reactions (MCRs) offer a powerful approach, as they integrate three or more reactants into a sole product one step with high atom economy [1,2]. Among them, the base-catalyzed MCR of aryl aldehydes, malononitrile, and ethyl acetoacetate is a well-established route to 4H-pyrans (**1**) (Figure 1) [3].

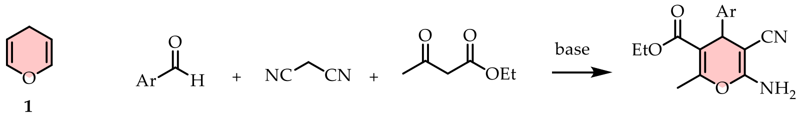


Figure 1. Base-catalyzed MCR synthesis of 4H-pyranes **1**.

In recent years, multicomponent reactions (MCRs) have gained prominence in the synthesis of complex fluorophore-based molecules [4]. To assess their potential, we applied this strategy to the preparation of 4H-pyrans, a heterocyclic family with notable biological and pharmaceutical relevance. Formylaryl-substituted BODIPY derivatives (**2**) were first obtained via the Liebeskind–Srogl cross-coupling (LSCC) reaction and subsequently reacted with malononitrile and ethyl acetoacetate to yield a series of emissive 4H-pyrans (Figure 2).

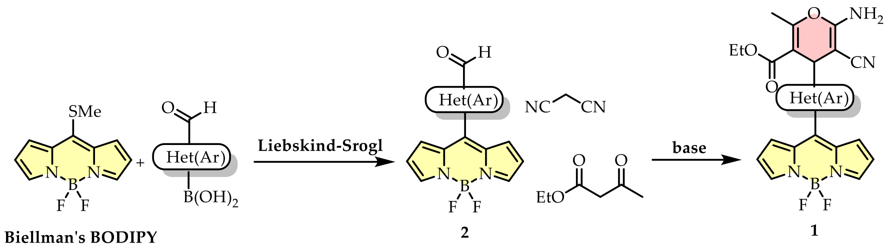
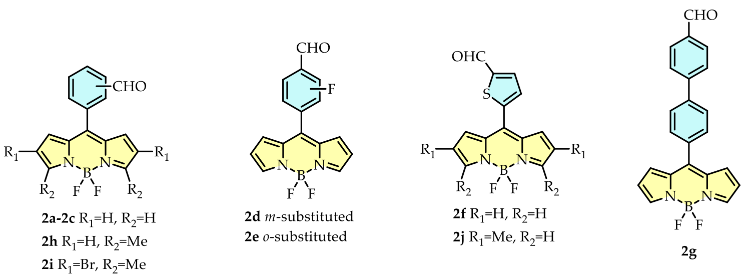


Figure 2. Synthetic strategy for achieving BODIPY-4H-Pyran hybrids.

We report a new strategy for the synthesis of 4H-pyran–BODIPY derivatives through a multicomponent reaction conducted in a surfactant-free EtOH/water medium. Nine compounds were obtained under conventional stirring in good yields (25–72%) over 4–24 h. Under ultrasound-assisted conditions, comparable yields (35–64%) were achieved with a significant reduction in reaction time (0.5–1.5 h).

2. Results and Discussion

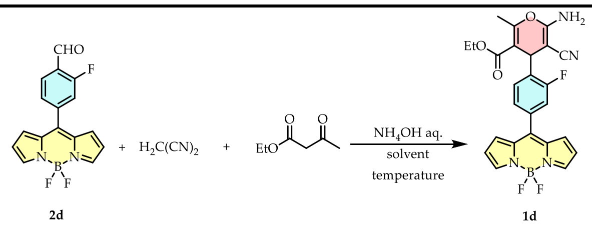
Biellmann's BODIPY was employed as the synthetic platform to access formylaryl-substituted derivatives via palladium-catalyzed Liebeskind–Srogl (LSCC) and Suzuki–Miyaura (SMCC) cross-coupling reactions (Scheme 1) [5]. The aldehydes **2a–j** were obtained in short reaction times (0.5–4 h) with good yields (71–98%). For **2g**, a two-step sequence was required: LSCC provided *meso*-(4-bromophenyl)BODIPY in 84% yield (1 h), followed by SMCC to give aldehyde **2g** in 94% yield (24 h). Aldehyde **2i** was prepared from 3,5-dimethyl-8-methylsulfanylBODIPY in 67% yield.



Scheme 1. Formylaryl-containing BODIPYs synthetized.

Optimization of the MCR was carried out with aldehyde **2d** (Table 1). Pyran **1d** was obtained in 72% yield in EtOH/H_2O at room temperature after 4 h (entry 1). Performing the reaction under reflux gave a comparable yield (70%, entry 2). As the results were similar, the milder conditions of entry 1 were selected for subsequent scope and limitation studies.

Table 1. Optimization of multicomponent reaction.

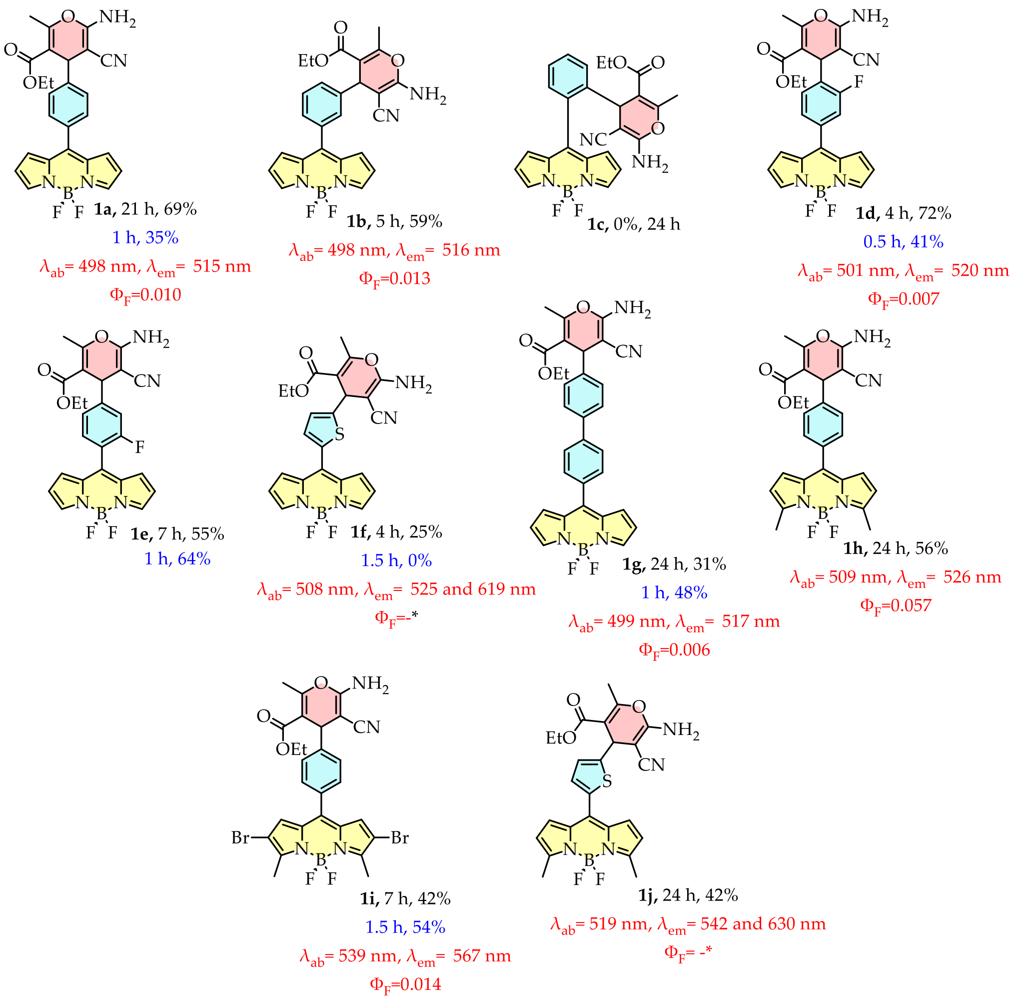


Entry	Solvent	Temperature	Time	Yield (%) [1]
1	EtOH/water	r.t.	4 h	72 (83) [2]
2	EtOH/water	reflux	4 h	70

[1] Isolated yield. [2] % Conversion determined by ^{1}H NMR.

With the optimized conditions in hand, the scope and limitations of the MCR were examined at room temperature (method A) and ultrasonic activation (method B). Method A afforded fluorescent 4H-pyrans (**1a–j**) in moderate to good yields (25–72%) over 4–24 h. Reactions were generally clean and more efficient with electron-withdrawing substituents on the aldehyde. Under method B, some of same products were obtained in moderate yields (35–64%) but with a drastic reduction in reaction times (0.5–1.5 h).

In general compounds **1a–j** have had low quantum efficiency (**Φ_F** = 0.61–5.67%) where **1g** was the lowest and **1i** was the highest. Although, for all products absorption and emission maxima was in accord with BODIPY characteristics. Direct meso-functionalization with aryl substituent has demonstrated affect directly quantum yield where products did not emit light efficiently as well as absorb it because of promotion of deactivation across nonradiative decay channels (Scheme 2) [6].



Scheme 2. Scope and limitations of BODIPY-4H-pyrans synthesis by MCR and its optical properties. **Method A**: 3 (1 equiv.), malononitrile (1 equiv.), ethyl acetoacetate (1 equiv.), NH_4OH (1 equiv.), ethanol, room temperature. **Method B:** 3 (1 equiv.), malononitrile (1 equiv.), ethyl acetoacetate (1 equiv.), NH_4OH (1 equiv.), ethanol, sonication (42 kHz). **Optical properties:** λ_{ab} = absorption maximum, λ_{em} = emission maximum, Φ_F = fluorescence quantum yield estimated in MeOH using the parent Borondipyrromethene (Φ_F = 80.8% in EtOAc) as standard [7]. * Fluorescence quantum yield is not given because two overlapped emission bands are detected simultaneously.

3. Conclusions

In summary, a series of fluorescent 4H-pyrans was synthesized via a multicomponent reaction of formyl-substituted BODIPYs, malononitrile, ethyl acetoacetate, and ammonium hydroxide. The key aldehyde precursors were readily obtained by LSCC and Suzuki cross-couplings. Two methods were evaluated: (A) conventional heating, which afforded good yields but was sensitive to steric effects, and (B) ultrasound-assisted conditions, which provided shorter reaction times and an environmentally friendly alternative, albeit with lower isolated yields.

4. Experimental Section

4.1. Generalities

Starting materials and reagents were commercially available unless otherwise stated. Solvents were distilled and dried by standard procedures. Reactions were carried out in oven- or flame-dried glassware, without inert atmosphere unless noted. Progress was monitored by TLC on silica gel F-254 plates under UV (254/365 nm). Flash chromatography was performed on silica gel Kieselgel 60 (70–230 mesh) with hexanes/ethyl acetate mixtures. ^{1}H and ^{13}C NMR spectra were recorded at 400/500 MHz and 101/126 MHz, respectively, in $CDCl_3$ or DMSO-d_6, using TMS, residual $CHCl_3$ or residual DMSO as internal references. Chemical shifts are reported in δ (ppm), multiplicity [br, s, d, t, q, sex, hep, m, exch, app], coupling constants *J* (Hz), and integration. A Branson 1510 ultrasonic bath was used for the synthesis of final compounds. Biellmann's BODIPY derivatives were purchased from Cuántico de México.

4.2. Spectroscopy

UV–vis and fluorescence spectra were recorded in methanol using spectroscopic-grade solvents and a 10 mm quartz cuvette. Emission was measured at λ_{exc} = 485 nm. Quantum yields (Φ_F) were determined relative to the parent BODIPY standard (Φ_{std} = 0.808 in EtOAc) using integrated emission vs absorbance plots, applying the refractive index correction (η_{MeOH} = 1.329).

*4.3. General Procedure for Products **1a–j***

4.3.1. Method A

BODIPY **2a–j**, malononitrile, ethyl acetoacetate, and NH_4OH were reacted in EtOH at room temperature; products were purified by column chromatography to give **1a–j** as colored powders.

4.3.2. Method B

BODIPY **2a–j**, malononitrile, ethyl acetoacetate, and NH_4OH were reacted in EtOH under ultrasound irradiation at room temperature; products were isolated by column chromatography as colored powders.

*4.4. Characterization of Products **1a–j***

1a. TLC (25% AcOEt/hexanes, R_f = 0.16); m.p. 203.3–205.2° C. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.12 (s, 2H), 7.65 (d, J = 7.8 Hz, 2H), 7.39 (d, J = 7.9 Hz, 2H), 7.03 (s, 2H), 6.98 (d, J = 3.4 Hz, 2H), 6.68 (s, 2H), 4.45 (s, 1H), 4.11–3.93 (m, 2H), 2.36 (s, 3H), 1.03 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d6) δ 165.33, 158.71, 157.60, 148.23, 146.76, 144.65, 131.72, 131.70, 131.54, 131.02, 127.53, 119.32, 106.70, 60.27, 56.65, 18.30, 13.75.

1b. TLC (25% AcOEt/hexanes, R_f = 0.25); m.p. 197.2–198.5° C. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.94 (s, 2H), 7.46 (dt, J = 3.2, 1.6 Hz, 3H), 7.41 (s, 1H), 6.94 (d, J = 3.4 Hz, 2H), 6.55 (d, J = 3.9 Hz, 2H), 4.55 (s, 3H), 4.14–4.01 (m, 2H), 2.38 (s, 3H), 1.08 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 165.62, 157.58, 157.31, 144.52, 144.13, 134.10, 130.03, 129.95, 129.40, 128.83, 118.72, 107.43, 61.63, 60.84, 38.80, 18.51, 14.01.

1d. TLC (25% AcOEt/hexanes, R_f = 0.16); m.p. 235–237.6° C. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.15 (s, 2H), 7.57 (dd, J = 10.7, 1.5 Hz, 1H), 7.48 (dd, J = 7.9, 1.6 Hz, 1H), 7.42 (d, J = 7.7 Hz, 1H), 7.07 (s, 2H), 6.99 (d, J = 4.0 Hz, 2H), 6.69 (dd, J = 4.2, 1.8 Hz, 2H), 4.74 (s, 1H), 4.09–3.93 (m, 2H), 2.38 (s, 3H), 1.01 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d6) δ 165.51, 159.08, 145.66, 145.31, 135.12, 134.99, 134.47, 133.79, 133.68, 132.15, 130.48, 127.53, 120.00, 118.26, 118.02, 105.67, 60.71, 55.75, 33.14, 18.76, 14.11.

1e. TLC (25% AcOEt/hexanes, R_f = 0.25); m.p. 253–255.5° C. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.15 (s, 2H), 7.61 (t, J = 7.7 Hz, 1H), 7.30–7.19 (m, 2H), 7.08 (s, 2H), 6.89 (d, J = 3.8 Hz, 2H), 6.67 (dd, J = 4.2, 1.7 Hz, 2H), 4.48 (s, 1H), 4.13–3.94 (m, 2H), 2.37 (s, 3H), 1.03 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d6) δ 165.22, 160.10, 158.74, 158.14, 150.90, 145.68, 139.73, 134.43, 132.61, 131.30, 123.48, 119.55, 115.01, 114.80, 106.13, 60.30, 56.30, 18.35, 13.77.

1f. TLC (25% AcOEt/hexanes, R_f = 0.23); m.p. 229.6–233° C. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.10 (s, 2H), 7.72 (d, J = 3.8 Hz, 1H), 7.36 (d, J = 4.0 Hz, 2H), 7.23 (s, 2H), 7.16 (d, J = 3.8 Hz, 1H), 6.73 (dd, J = 4.1, 1.7 Hz, 2H), 4.80 (s, 1H), 4.21–4.07 (m, 2H), 2.34 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d6) δ 159.43, 158.20, 157.59, 144.14, 131.87, 126.31, 119.21, 106.69, 60.66, 55.96, 34.24, 18.42, 13.88.

1g. TLC (25% AcOEt/hexanes, R_f = 0.22); m.p. 230–232.7° C. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.96 (s, 2H), 7.77–7.61 (m, 6H), 7.38 (d, J = 8.1 Hz, 2H), 7.00 (dd, J = 10.3, 3.5 Hz, 2H), 6.57 (s, 2H), 5.70 (s, 2H), 4.84 (s, 1H), 4.17 (q, J = 7.0 Hz, 2H), 2.63 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 145.28, 144.41, 142.52, 141.40, 131.62, 131.57, 131.35, 129.78, 129.45, 128.19, 128.12, 127.34, 127.23, 118.78, 61.47, 48.16, 42.15, 19.48, 14.23.

1h. TLC (25% AcOEt/hexanes, R_f = 0.27); m.p. 236.3–238.8° C. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.36 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 8.1 Hz, 2H), 6.63 (d, J = 4.1 Hz, 2H), 6.19 (d, J = 4.1 Hz, 2H), 4.48 (s, 3H), 4.11–3.94 (m, 2H), 2.57 (s, 6H), 2.35 (s, 3H), 1.05 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 165.65, 157.67, 157.53, 157.45, 145.89, 142.22, 134.47, 133.04, 130.74, 127.38, 118.74, 107.60, 61.93, 60.81, 38.65, 29.71, 18.55, 14.90, 13.99.

1i. TLC (25% AcOEt/hexanes, R_f = 0.38); m.p. 200–203.5° C. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.59 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 7.03 (s, 2H), 6.96 (s, 2H), 4.44 (s, 1H), 4.11–3.94 (m, 2H), 2.54 (s, 6H), 2.36 (s, 3H), 1.03 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d6) δ 165.30, 158.77, 157.60, 154.81, 148.12, 132.37, 130.99, 130.64, 130.63, 119.68, 108.60, 106.75, 60.26, 56.60, 18.31, 13.18.

1j. TLC (25% AcOEt/hexanes, R_f = 0.34); m.p. 232.5–235.6° C. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.25 (d, J = 3.7 Hz, 1H), 7.05 (d, J = 4.0 Hz, 2H), 7.00 (d, J = 3.6 Hz, 1H), 6.29 (d, J = 4.1 Hz, 2H), 4.87 (s, 1H), 4.64 (s, 2H), 4.20 (tdt, J = 14.3, 10.9, 5.4 Hz, 2H), 2.64 (s, 6H), 2.39 (s, 3H), 1.24 (t, J = 7.1 Hz, 4H). ^{13}C NMR (126 MHz, Chloroform-d) δ 165.36, 158.30, 157.82, 157.49, 153.14, 134.79, 133.92, 133.73, 131.80, 125.34, 119.38, 118.46, 107.70, 61.14, 34.08, 18.66, 14.95, 14.11.

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