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Fluorene-Based Multicomponent Reactions

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Dedicated to Professor Ioulia Stephanidou-Stephanatou for her contributions to heterocyclic chemistry

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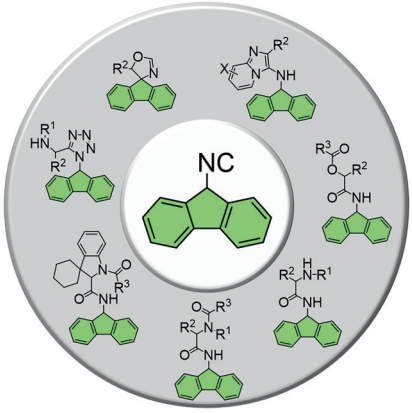

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Abstract Fluorene and fluorenone are privileged structures with extensive utility in both materials science and drug discovery. Here, we describe syntheses of those moieties through isocyanide-based multicomponent reactions (IMCRs) and the incorporation of the products in diverse and complex derivatives that can be further utilized. We performed six different IMCRs, based on the dual functionality of 9-isocyano-9*H*-fluorene, and we describe 23 unprecedented adducts.

Key words fluorene, fluorenone, multicomponent reactions, Ugi reaction, isocyanofluorene, spiro compounds

Assistant Professor Constantinos G. Neochoritis received his PhD in Organic Chemistry under the guidance of Professors J. Stephanidou Stephanatou and C. Tsoleridis in the Department of Chemistry at Aristotle University of Thessaloniki, Greece in 2011. Being fascinated by the applied multicomponent reaction (MCR) chemistry, he joined the research group of Prof. Alexander Dömling in the Drug Design Group at the University of Groningen for his postdoctoral studies, whereas in 2014 he cofounded the biotech company TelesisPharma. In 2019, he was appointed as assistant professor in the chemistry department of University of Crete, Greece. His research interests include bioactive heterocycles, multicomponent reactions, novel materials and high throughput synthesis. He has published more than 50 peer-reviewed papers and book contributions.

Fluorene derivatives have traditionally been at the epicenter of many research studies in various fields from optoelectronics[1] and solar cells[2] to synthetic[3] and medicinal chemistry.[4] The unique electronic properties of fluorenes make it highly interesting to study their charge-transfer complexes as electron-deficient candidates with semiconducting and photoconducting properties and as electron-transport materials (Figure 1A).[1,2,5] Fluoren-9-one, in particular, is considered to be a privileged structure, as it is relatively planar with high thermal stability and good electron-transport properties. Many of its derivatives exhibit both aggregation-induced emission and bathochromic solid-state fluorescence.[6]

In addition, the fluorene structural motif is present in many natural products and bioactive compounds.[7] For example, dendroflorin (from *Dendrobium densiflorum*) is a natural product with high antioxidant activity,[8] and caulophine (from the radix of *Caulophyllum robustum* Maxim.) shows antimyocardial ischemia activity (Figure 1A).[9] Moreover, fluorene derivatives have been reported as effective inhibitors, for example of cyclophorin A,[4] fibril formation of human transthyretin,[10] or glycoside hydrolases (Figure 1B).[11,12] Finally, fluorene derivatives have been utilized in synthetic organic chemistry in the archetypical protective group Fmoc.[13] For these reasons, multiple synthetic ways to access fluorene derivatives, including one-pot strategies and catalysts, have been reported.[14–22]

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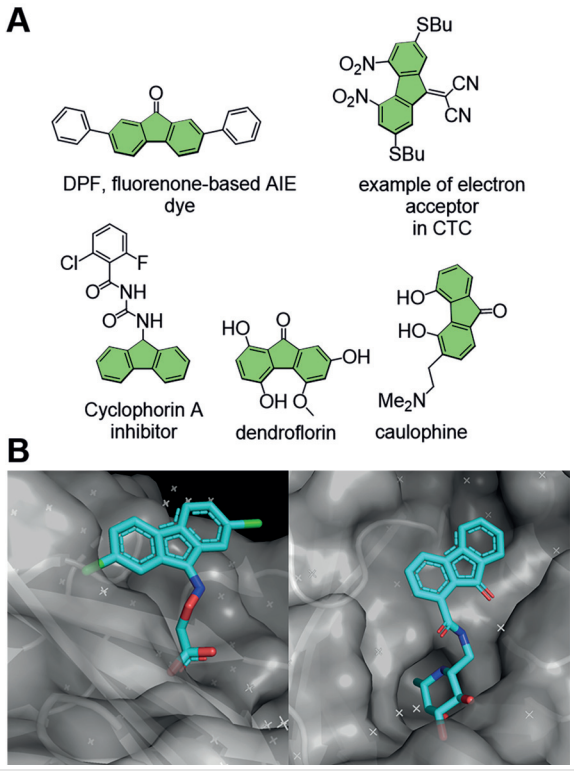
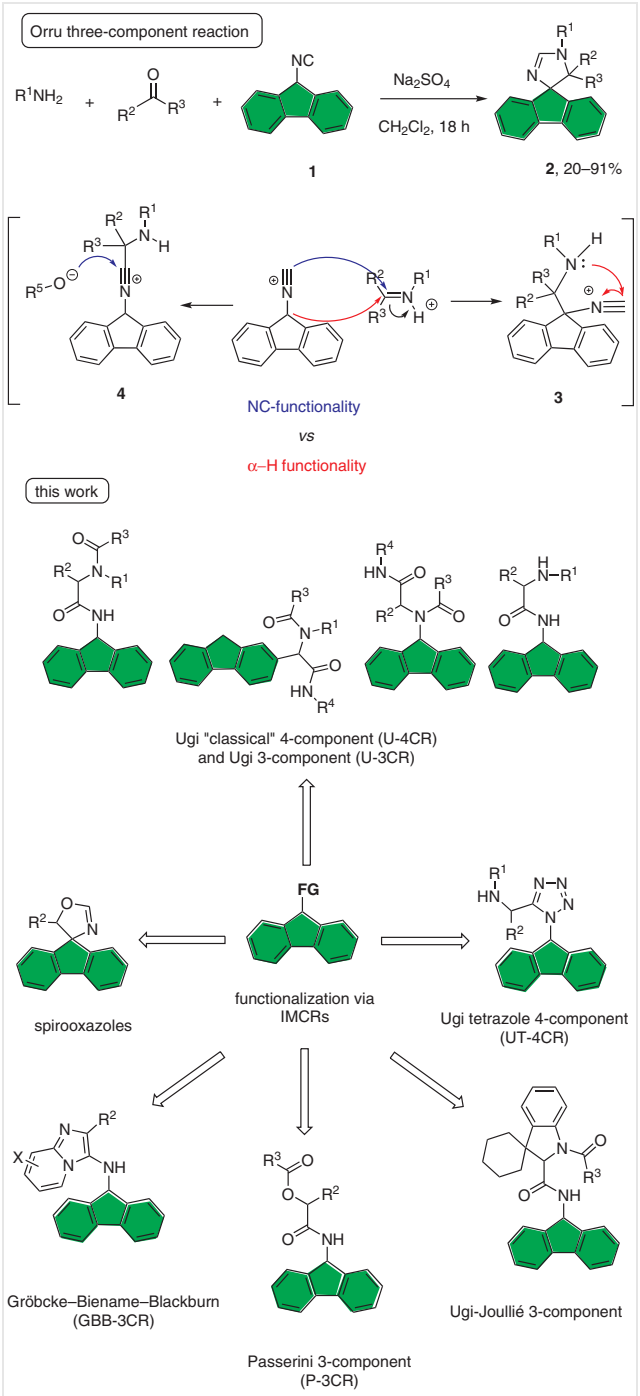


Figure 1 A. Fluorene-based derivatives in applied materials and natural products; B. Fluorene-based molecules in drug discovery: Left: inhibitor of transthyretin [Protein Data Bank identifier (PDB ID): 5E4A]; Right: α-L-fucosidase inhibitor (PDB ID: 2XII).

Multicomponent reactions (MCRs) are powerful tools for one-step assembly, functionalization, and transformation of molecules. They can accelerate the exploration of chemical space and improve the sustainability of the chemical enterprise.[23] A very important and diverse class of MCRs are the isocyanide-based MCRs (IMCRs),[24] in which a versatile isocyanide moiety is added to the final product.[25,26]

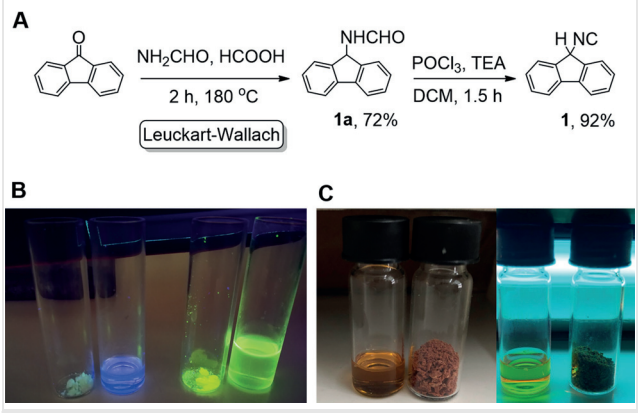
The incorporation of fluorene derivatives by MCRs to give adducts with many points of diversification is of high importance, but is quite underexplored and limited in scope.[27–32] Structural diversity and complexity in such libraries are critical to the elucidation of structure–activity relationships that drive the development of new products and technologies. Orru and co-workers,[33] in their pioneering work, took advantage of the α-acidic nature of 9-isocyano-1*H*-fluorene (**1**; pK_a = 12.3 in DMSO), which becomes aromatic after deprotonation,[34–36] and were able to synthesize the druglike spiro-2-imidazolines **2** through a three-component reaction, now known as the Orru reaction (Orru-3CR; Scheme 1).[33,37–39] Due to the acidic nature of the isocyanide, in which the isocyano functionality competes with α-H acidity, the Mannich-type intermediate **3** is probably formed. Intramolecular attack by the nucleophilic amine on the isocyanide carbon of **3** is the driving force toward cyclization to give fluoreno-2-imidazolines **2** (Scheme 1; red arrows).[33]



Scheme 1 α-H versus NC functionality of the isocyanofluorene **1** yielding the Orru-3CR, and our proposed IMCR-based use of fluorenes, including the synthesis of spirooxazoles

In this work, we elaborate the fluorene moiety by its incorporation into various isocyanide-based MCRs. Our study was based primarily on 9-isocyano-1*H*-fluorene (**1**) as a versatile building block, and focused on the isocyano function (Scheme 1; blue arrows, intermediate **4**); in parallel, we investigated the formation of the 2-imidazolines under the appropriate conditions. For example, it has been reported that in an Ugi reaction setup, reducing the nucleophilicity of the nitrogen of the amine component might shift the reaction toward the classical pathway for bisamides (Scheme 1, intermediate **4**).[31,33] Taking this into account, we examined a series of IMCRs including the classical Ugi reaction and some of its main variants: the Ugi-tetrazole four-component reaction (U-4CR),[40] the Ugi three-component reaction (U-3CR),[41] the Ugi–Joullié reaction,[42] and the Ugi–Smiles four-component reaction,[43–45] along with the Groebke–Blackburn–Bienaymé (GBB-3CR)[46–48] and Passerini three-component (P-3CR) reactions.[49] Moreover, we were able to combine functions of the acidity and the isocyano moiety of 9-isocyano-9*H*-fluorene to permit access to spirooxazolidine derivatives.

We synthesized 9-isocyano-9*H*-fluorene (**1**) from 9*H*-fluoren-9-one by our recently described Leuckart–Wallach procedure[50] toward the corresponding formamide **1a** (Scheme 2A). The standard procedure[33] starts with the formylation of 9*H*-fluorene-9-amine, which is commercially available as its hydrochloride salt (CAS 5978-75-6) but is substantially more expensive than 9*H*-fluoren-9-one (CAS 486-25-9). Dehydration of formamide **1a** under the typical conditions afforded the required solid odorless starting material **1** on a gram scale in 92% yield. Notably, a solution of formamide **1a** in dichloromethane showed a characteristic bright-blue fluorescence on excitation at 366 nm (Scheme 2B), whereas the solution of isocyanide **1** in dichloromethane fluoresced light-green on excitation at 254 nm (Scheme 2C).



Scheme 2 (A) Access to the isocyanide **1** through the Leuckart–Wallach reaction of 9*H*-fluoren-9-one. (B) Fluorescence of 9*H*-fluoren-9-one (green color; right-hand vial) and formamide **1a** (blue color, left-hand vial) on excitation at 366 nm, both as a solid and as a solution in CH_2Cl_2. (C) Fluorescence of 9-isocyanofluorene on excitation by visible light (left) and at 254 nm (right) both as a solid and as a solution in CH_2Cl_2.

The classic U-4CR reaction is one of the most versatile transformations in organic chemistry. It gives access to huge libraries due to its four points of diversification, and it also serves as an excellent hub for a plethora of secondary transformations.[51,52] We employed both the isocyanide **1** and the fluorene-based aldehyde and amine to obtain the corresponding bisamides **5a–c** in yields of 34-89%, respectively. Notably, in the case of **5c**, three molecules of fluorene were incorporated into one adduct, demonstrating a favorable architectural aspect of this reaction (Figure 2). Interestingly, when we switched to aliphatic aldehydes such as

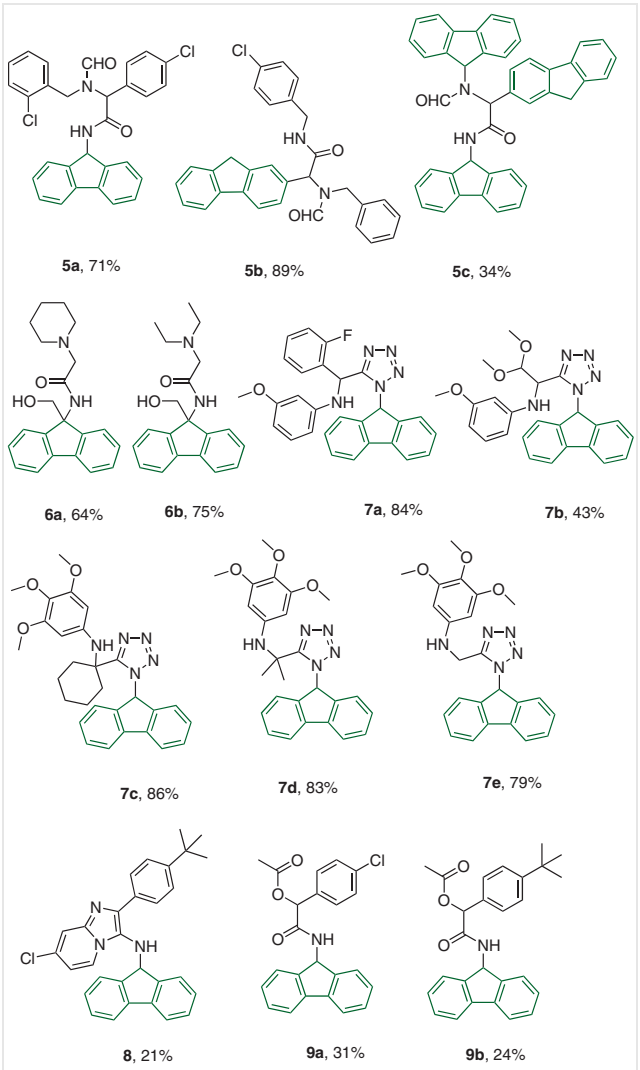


Figure 2 Syntheses of U-4CR (**5a–c**), U-3CR (**6a** and **6b**), UT-4CR (**7a–e**), GBB-3CR (**8**), and P-3CR (**9a** and **9b**) adducts by utilizing fluorene moieties as isocyanide, aldehyde, and amine components

5-chloropentanal, and thereby increased the nucleophilicity of the nitrogen of the amine, the corresponding 2-imidazoline **2a** was obtained (Figure 3).

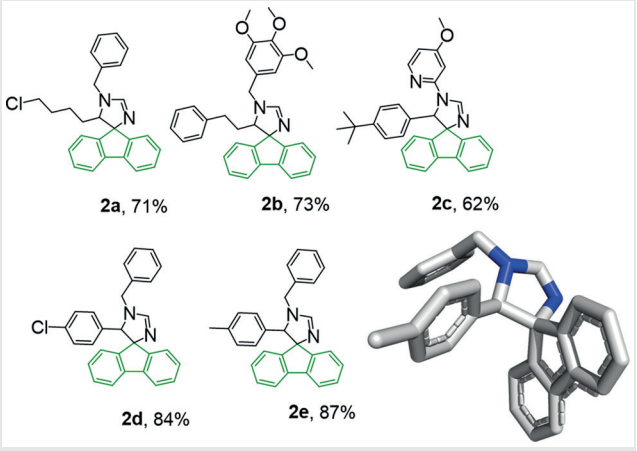


Figure 3 Synthesis of imidazolines **2a–e** by an Orru-3CR, and the X-ray structure of compound **2e** (CCDC 2065539)

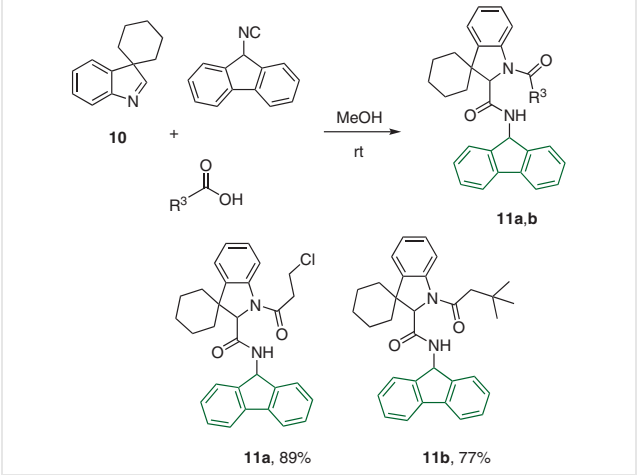
The Ugi three-component reaction (U-3CR) is a variant of the Ugi reaction in which water plays the role of nucleophile. Often, the resulting α-aminoacylamides which are present in many bioactive compounds and commercially available drugs, lead to improved pharmacokinetic/pharmacodynamic properties, including oral bioavailability and water solubility, due to the incorporation of a basic amine.[53] We therefore investigated the U-3CR that gave the α-aminoacylamides **6a** and **6b** (Figure 2). We employed secondary amines in an aqueous solution of formaldehyde with no catalysts, additives, or other solvents to access caine-type adducts. It was observed that an additional molecule of formaldehyde was added as a hydroxymethylene moiety in a Mannich-type addition. This was attributed to the acidic proton of the fluorene moiety and to the aqueous reaction conditions.

The Ugi-tetrazole variant (UT-4CR) is one of the most well-known and well-studied variants of the Ugi reaction. It gives easy access to tetrazole derivatives, which are very important bioisosteres of carboxylic acid and *cis*-amide moieties. Moreover, they have enhanced metabolic stability and other beneficial physicochemical properties.[54] We used a variety of aryl amines, aldehydes, and ketones, which all yielded the desired fluorene–tetrazole compounds **7a–e** in good to excellent yields (Figure 2). Compounds **7a** and **7b** bear additional functional groups that can allow various subsequent modifications (e.g., S_NAr reactions and deprotection of the acetal group). Interestingly, when we employed 3-phenylpropanal in combination with 3,4,5-trimethoxybenzylamine, the corresponding imidazoline **2b** was formed (Figure 3).

In the last twenty years, the Groebke–Blackburn–Bienaymé reaction (GBB-3CR) has emerged as one of the most important MCRs.[55–57] The resulting imidazo[1,2-*a*]heterocycles with diverse substitution patterns are a prime class of heterocycles present in many commercially available drugs and drugs in late-stage clinical trials.[58] We have performed a GBB reaction with 4-chloropyridin-2-amine, yielding the adduct **8** (Figure 2). Interestingly, when we employed 4-methoxypyridin-2-amine, the imidazoline **2c** was obtained, highlighting the aforementioned mechanistic assumptions (Figure 3). Notably, an Ugi–Smiles reaction that we attempted as an additional Ugi variant afforded the imidazolines **2d** and **2e** as the sole products. In support of this, we solved the crystal structure of compound **2e**, proving the different pathway taken by the reaction (Figure 3).[59]

The Passerini reaction (P-3CR) belongs to the classic repertoire of MCR chemistry, as it provides easy access to α-acyloxy carboxamides. We attached a fluorene moiety to a Passerini scaffold to give compounds **9a** and **9b** (Figure 2). We used acetic acid as the acid component, together with substituted aromatic aldehydes containing electron-donating or electron-withdrawing groups.

The Ugi–Joullié reaction[42] is an extremely versatile cyclic variant of the Ugi reaction that yields conformationally constrained peptidomimetics and antibacterial depsipeptides.[60] It utilizes a preformed C=N bond in a three-component setup, and it has been widely used in various secondary transformations after an initial multicomponent reaction.[61] Hence, we synthesized the spiroindolenine **10**, which is attractive due to its 3D character,[62] through a Fischer indole synthesis, and we performed its Ugi–Joullié reaction with 9-isocyano-9*H*-fluorene (**1**). The reaction proceeded smoothly, yielding the adducts **11a** and **11b** (Scheme 3).



Scheme 3 Synthesis of Ugi–Joullié adducts **11a** and **11b** by using 9-isocyano-9*H*-fluorene (**1**)

In recent years, there has been great interest in increasing the number of 3D-shaped alicyclic building blocks in drug discovery ('escape from Flatland'), and spiro compounds are of high importance.[63,64] For this reason, we were interested in combining the α-acidity of isocyanide **1** with its isocyano functionality; we therefore subjected it to reaction with an aldehyde in a similar fashion to the van Leusen oxazole synthesis using tosylmethyl isocyanide (TosMIC).[65] To our delight, the reaction proceeded under mild conditions to give the required spirooxazolidines **12a–c** in good to excellent yields after treatment with K_2CO_3 at room temperature (Scheme 4). Furthermore, we solved the crystal structure of compound **12c** (Scheme 4).[59]

In conclusion, we have synthesized 23 new derivatives based on ten different scaffolds by functionalizing a fluorene building block through an MCR-based array of reactions.[66,67] We have demonstrated the potential of MCR chemistry by utilizing this privileged scaffold of proven interest in materials science and drug discovery. We envision that our strategy will add to the arsenal of synthetic methods for materials containing fluorene moieties.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1471-9080.

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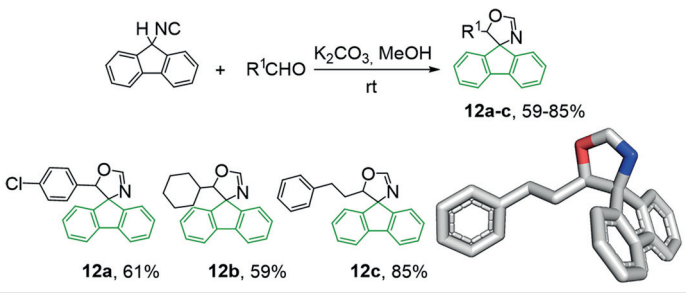

Scheme 4 Synthesis of the spirooxazolidines **12a–c**, and the X-ray structure of **12c** (CCDC 2065540)

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(66) **Ugi-Tetrazole Four-Component (UT-4CR) Synthesis of 7a–e and 2b; General Procedure**
The appropriate aniline (1.0 mmol), isocyanide (1.0 mmol), and trimethylsilyl azide (1.0 mmol) were added to a stirred solution of the appropriate aldehyde (1.0 mmol) in MeOH (1.0 mL) at rt, and the mixture was stirred vigorously for 1–2 h. Half the solvent was removed under reduced pressure and, if a solid residue appeared, it was collected by filtration and washed with Et_2O. Alternatively, the solvent was removed under reduced pressure, and the residue was purified by column chromatography [silica gel, PE–EtOAc (1:1)].
***N*-{1-[1-(9*H*-Fluoren-9-yl)-1*H*-tetrazol-5-yl]cyclohexyl}-3,4,5-trimethoxyaniline (7c)**
Gray solid; yield: 427 mg (86%); mp 216–218 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.94 (d, *J* = 7.6 Hz, 2 H), 7.44 (t, *J* = 7.6 Hz, 2 H), 7.26 (s, 1 H), 7.12 (s, 2 H), 6.39 (s, 2 H), 5.72 (s, 2 H), 3.59 (s, 3 H), 3.47 (s, 6 H), 2.87 (s, 1 H), 2.61–2.58 (m, 2 H), 2.352–2.348 (m, 2 H), 1.80–1.69 (m, 5 H), 1.47–1.44 (m, 1 H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 160.3, 153.6, 141.6, 141.5, 140.0, 129.7, 129.5, 128.0, 124.1, 120.8, 91.6, 61.9, 60.5, 55.5, 53.5, 45.5, 24.8, 20.9. MS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{29}H_{31}N_5NaO_3$: 520.23; found: 520.07.
(67) **Oxazoles 12a–c; General Procedure**
K_2CO_3 (1.5 mmol) was added to a stirred solution of the appropriate aldehyde (1.0 mmol) and 9-isocyano-9*H*-fluorene (**1**; 1.0 mmol) in MeOH (3.0 mL) at rt, and the mixture was stirred vigorously for 1–5 h. The solvent was then removed under reduced pressure and the residue was collected by filtration and washed with Et_2O. Alternatively, the solvent was removed under reduced pressure and the residue was purified by column chromatography [silica gel, PE–EtOAc (4:1)].
5′-(2-Phenylethyl)spiro[fluorene-9,4′-[1,3]oxazole] (12c)
White solid; yield: 276 mg (85%); mp 161–163 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.89–7.83 (m, 2 H), 7.69 (s, 1 H), 7.43–7.27 (m, 6 H), 7.10–7.05 (m, 3 H), 6.76 (d, *J* = 6.9 Hz, 2 H), 4.68–4.65 (m, 1 H), 2.30–2.25 (m, 1 H), 2.13–2.07 (m, 1 H), 1.89–1.88 (m, 1 H), 1.32–1.28 (m, 1 H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 158.2, 148.1, 143.5, 140.6, 140.0, 139.9, 129.0, 128.9, 128.23, 128.18, 128.0, 127.4, 126.0, 125.9, 124.5, 120.5, 120.2, 85.1, 80.6, 32.9, 31.5. MS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{23}H_{19}NNaO$: 348.14; found: 348.10.