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Facile one-pot synthetic access to libraries of diversely substituted 3-aryl (Alkyl)-coumarins using ionic liquid (IL) or conventional base/solvent, and an IL-mediated approach to novel coumarin-bearing diaryl-ethynes

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ABSTRACT

The *in-situ* formed carbonylimidazole derivatives of Ar(alkyl)-CH_2COOH react at r.t. with substituted salicylaldehydes in [BMIM][PF_6] or [BMIM][BF_4] as solvent, and [PAIM][NTf_2] as basic-IL, to produce libraries of 3-aryl(alkyl)coumarins. Whereas these reactions can also be performed with similar efficiency in THF by employing DBU, the IL approach offers easier work-up and recycling of the IL solvent. An IL-mediated approach to the synthesis of novel coumarin-bearing diaryl-ethynes by the Sonogshira reaction is also reported, and the potential for recycling/reuse of the IL solvent is shown.

Coumarins are important constituents of biologically active natural products and valuable building blocks in synthetic and medicinal chemistry [1–4], that have also found application in materials chemistry [5]. Substituted 3-arylcoumarins are of particular interest due to their diverse biological activity notably as anti-Alzheimer agents [6,7].

Drawbacks and limitations associated with the classical methods such as Pechman and Perkin reactions, have prompted the development of newer strategies for the synthesis of 3-arylcoumarins. These methods include oxidative ($KMnO_4$/AcOH) arylation of coumarins using arylboronic acids [8], Pd-catalyzed Suzuki coupling starting with 3-chlorocoumarins in DMF/H_2O/reflux [9], decarboxylative coupling using N-hydroxyphthalimide esters with $Ir(ppy)_3$/DMSO/TFA [10], and condensation of allenes with phenols and anisoles employing TfOH/DCE [11]. Among the methods that employ salicylaldehydes as reaction partner are condensation of salicylaldehydes with ynamides employing $ZnBr_2$ [12], reaction of N-acylbenzotriazoles with salicylaldehydes via acylation/cyclization [13], reaction of salicylaldehydes with phenylacetic acid using $POCl_3$/pyridine to form the benzyl ester followed by a base-catalyzed cyclization (KOH/pyridine) [14a], reaction of salicylaldehydes with substituted phenylacetic acids using cyanuric chloride/N-methylmorpholine/DMF/reflux [14b], and condensation of salicylaldehydes with aryl-substituted 1,1-dibromo-1-alkene [15].

In continuation of our studies on synthetic and catalytic chemistry in ILs [16], we sought to develop a simple IL-based one-pot method using readily available low cost reagents that enables the assembly of a library of 3-arylcoumarins under very mild conditions. By using [PAIM][NTf_2] as the basic-IL,[16e-g] and [BMIM][PF_6] or [BMIM][BF_4] as solvent, the *in-situ* formed carbonylimidazole derivatives of Ar(alkyl)-CH_2COOH, formed by reaction with carbonyl-diimidazole (CDI), smoothly reacted with salicylaldehyde at r.t. to furnish 3-aryl(alkyl)coumarins (Fig. 1). Following an initial feasibility study, the scope of the reaction was examined by employing diversely substituted salicylaldehydes and substituted phenylacetic acids, and the results are gathered in Table 1. Fig 2.

Further feasibility studies showed that this transformation could also be achieved with similar efficiency at r.t. by using BDU in THF; therefore the scope of the reaction was reexamined in order to provide a broader side-by-side comparison (Table 2).

Whereas the IL-based method and the conventional base/solvent method appear to have similar efficiency, the IL method is advantageous from a practical point of view due to easier

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0040-4039/

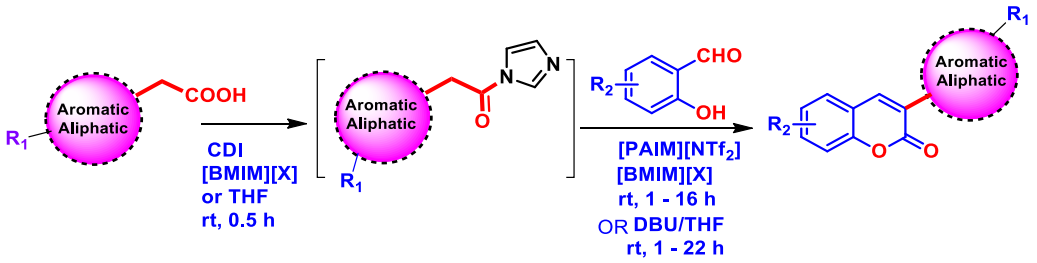

Fig. 1. Facile one-pot synthesis of a library of 3-arylcoumarins

Table 1
Synthesis of 3-aryl(alkyl)coumarins in IL

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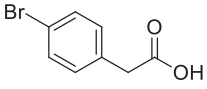
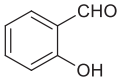
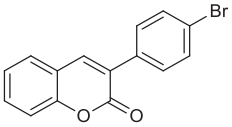
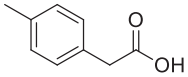
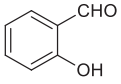
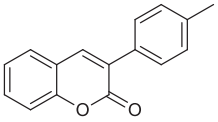
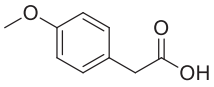
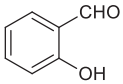
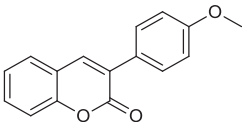
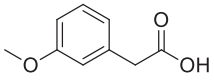
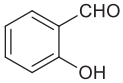
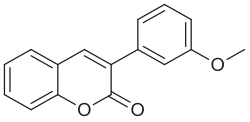
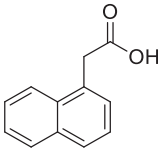
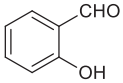
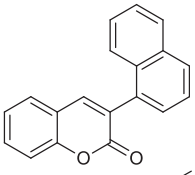
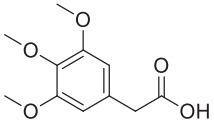
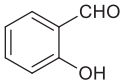
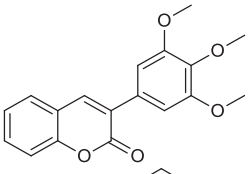
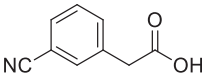
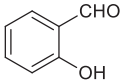
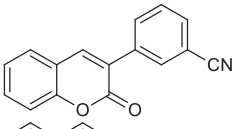
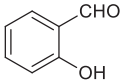
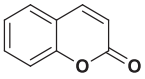
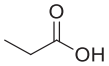
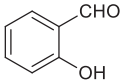
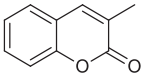
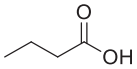
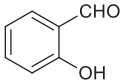
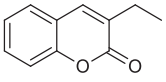
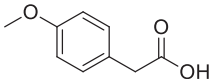
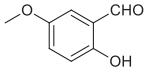
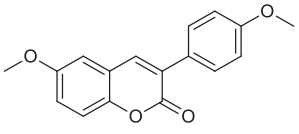
1				[BMIM][PF_6]	1	76[d]
2				[BMIM][PF_6]	1	68[e]
3				[BMIM][BF_4]	2	78[d]
4				[BMIM][PF_6]	1	68[f]
5				[BMIM][BF_4]	2	67[e]
6				[BMIM][BF_4]	1	77[d]
7				[BMIM][BF_4]	2	69[d]
8				[BMIM][PF_6]	12	54[e]
9				[BMIM][BF_4]	16	55[e]
10				[BMIM][BF_4]	6	61[e]
11				[BMIM][PF_6]	1	86[d]

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Table 1 (*continued*)

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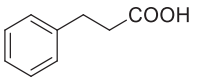
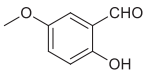
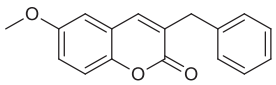
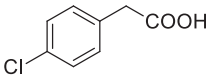
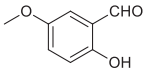
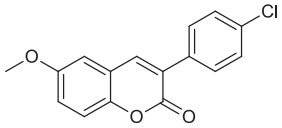
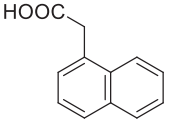
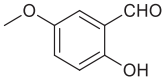
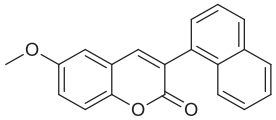
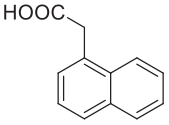
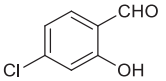
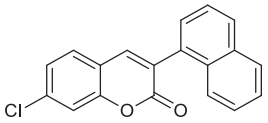
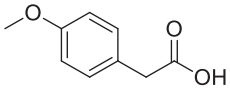
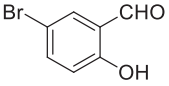
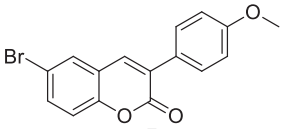
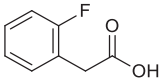
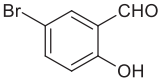
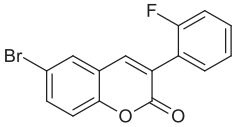
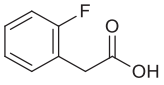
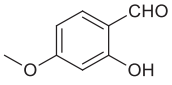
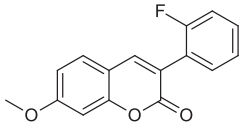
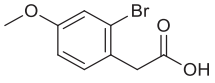
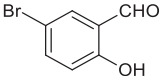
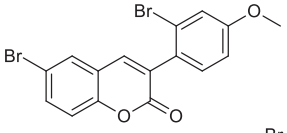
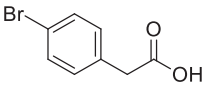
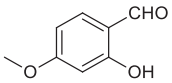
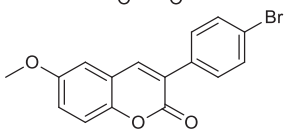
12				[BMIM][PF_6]	6	72[d]
13				[BMIM][BF_4]	1	69[d]
14				[BMIM][BF_4]	1	65[e]
15				[BMIM][BF_4]	2	68[e]
16				[BMIM][BF_4]	1	60[e]
17				[BMIM][PF_6]	3	66[e]
18				[BMIM][PF_6]	2	74[d]
19				[BMIM][BF_4]	4	70[d]
20				[BMIM][PF_6]	2	72[d]

[a] Reaction conditions: Ar(R)CH_2COOH (1 mmol), CDI (1.1 mmol), [BMIM][X] (10 -12 mL), Salicylaldehyde (1 mmol), [PAIM][NTf_2] (1.4 mmol); [b]room temperature; [c] Isolated yield of pure product; [d]Yield employing fresh IL; [e]Yield using recycled IL (2nd cycle); [f] Yield using recycled IL (3rd cycle).

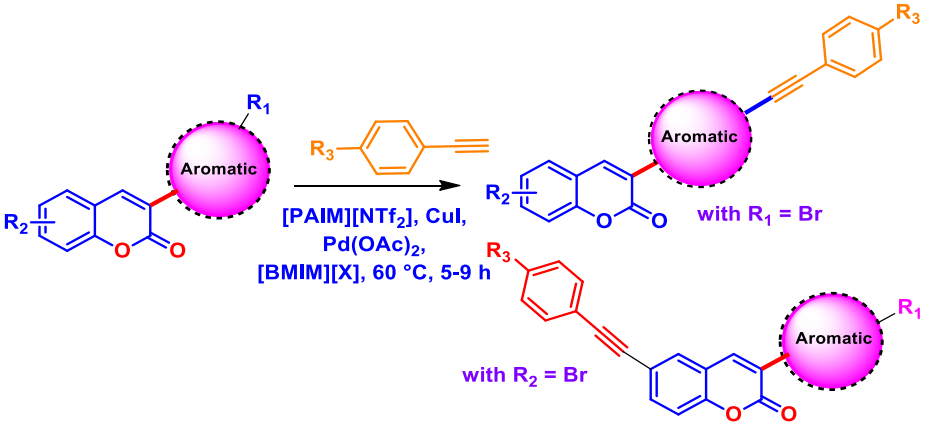


Fig. 2. IL-mediated one-pot sequential synthesis of coumarin-bearing diaryl-ethynes

Please cite this article as: P. Prabhala, H. M. Savanur, S. M. Sutar et al., Facile one-pot synthetic access to libraries of diversely substituted 3-aryl (Alkyl)-coumarins using ionic liquid (IL) or conventional base/solvent, and an IL-mediated approach to novel coumarin-bearing diaryl-ethynes, Tetrahedron Letters, https://doi.org/10.1016/j.tetlet.2020.151854

Table 2
Synthesis of 3-aryl(alkyl)coumarins in conventional base and solvent

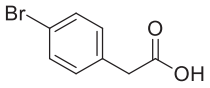
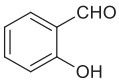
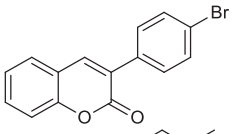
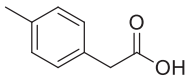
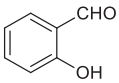
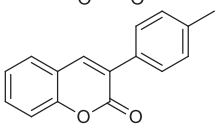
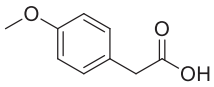
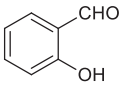
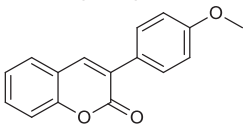
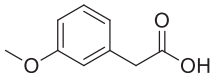
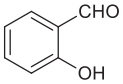
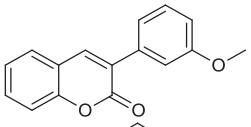
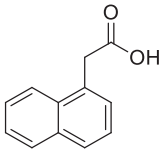
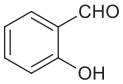
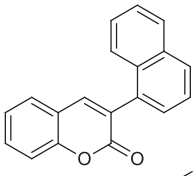
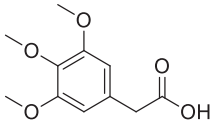
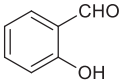
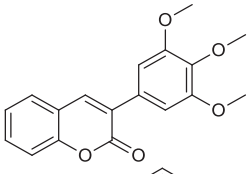
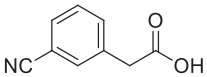
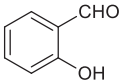
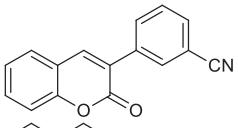
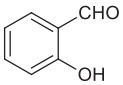
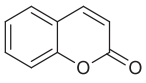
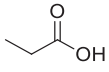
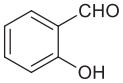
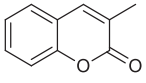
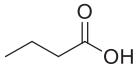
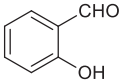
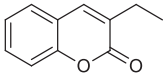
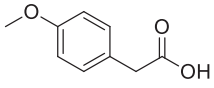
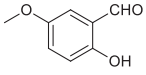
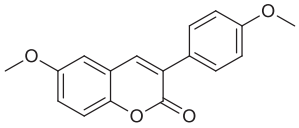
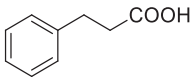
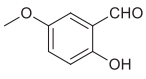
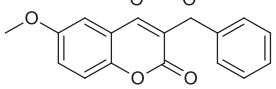
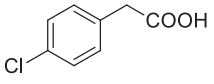
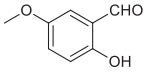
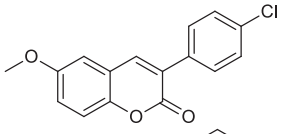
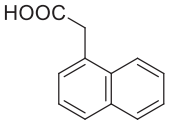
Run #	Ar(R)CH_2CO_2H	Salicylaldehyde	Product[a]	Solvent	Time[b][h]	Yield[c] [%]
21				THF	2	72
22				THF	1	64
23				THF	2	75
24				THF	1	63
25				THF	2	60
26				THF	2	73
27				THF	1	66
28				THF	12	55
29				THF	22	51
30				THF	8	60
31				THF	2	82
32				THF	12	65
33				THF	3	66
34				THF	4	55

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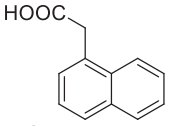
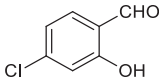
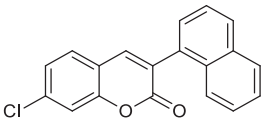
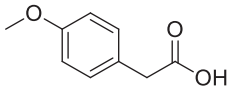
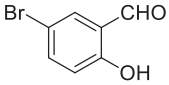
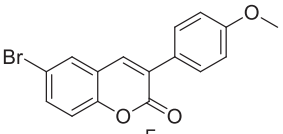
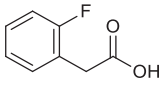
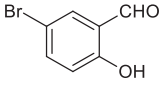
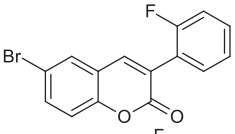
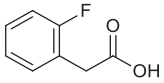
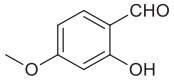
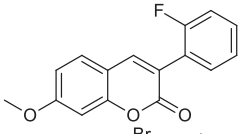
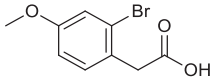
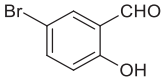
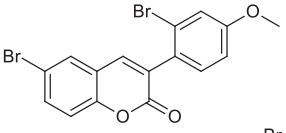
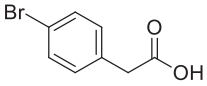
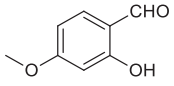
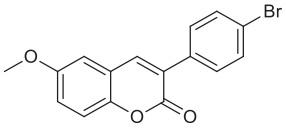
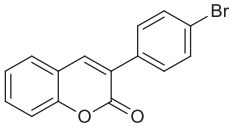
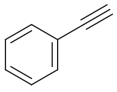
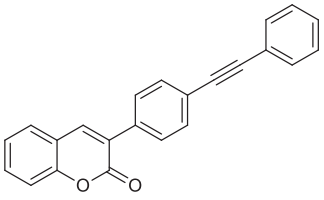
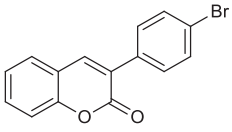
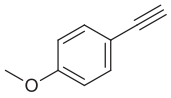
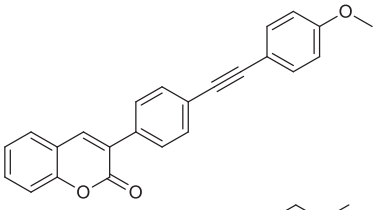
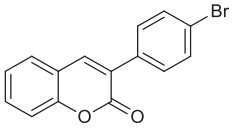
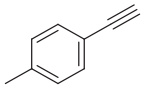
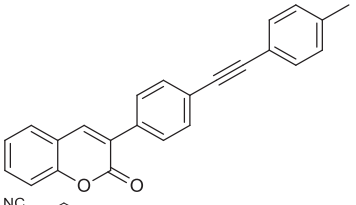
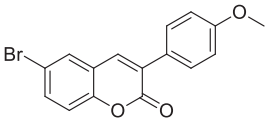
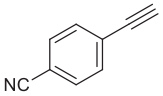
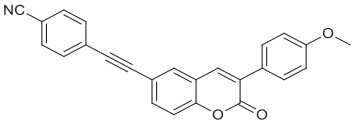
Table 2 (*continued*)

Run #	Ar(R)CH_2CO_2H	Salicylaldehyde	Product[a]	Solvent	Time[b][h]	Yield[c] [%]
35				THF	1	61
36				THF	1	68
37				THF	2	69
38				THF	1	74
39				THF	2	68
40				THF	1	61

[a] Reaction conditions: Acid (1 mmol), Salicylaldehyde (1 mmol), CDI (1.1 mmol), DBU (1.5 mmol), THF (10 mL); [b]room temperature; [c]Isolated Yield of pure products.

Table 3
Sequential IL-mediated synthesis of coumarin-bearing diaryl-ethynes

Run #	Coumarin	Aryl-ethyne	Product[a]	IL	Time[b] [h]	Yield[c] [%]
1				[BMIM][PF_6]	9	63
2				[BMIM][PF_6]	7	66
3				[BMIM][PF_6]	7	63
4				[BMIM][BF_4]	5	54

(*continued on next page*)

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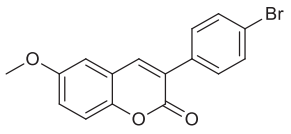
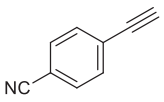
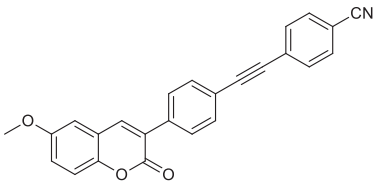
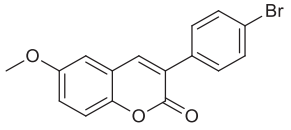
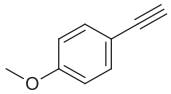
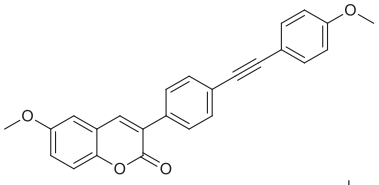
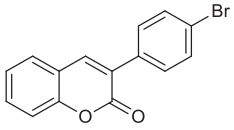
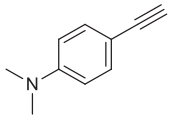
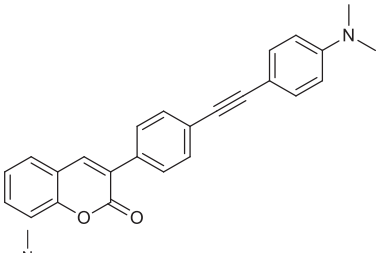
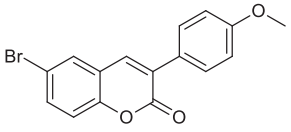
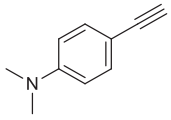
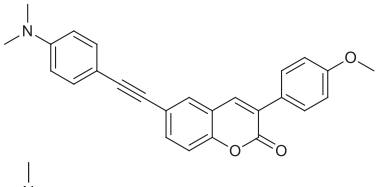
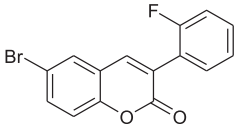
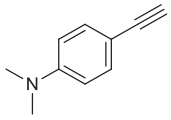
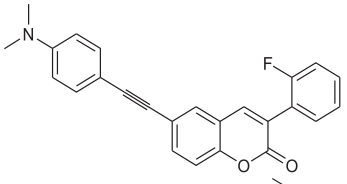
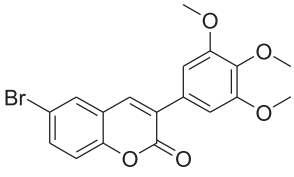
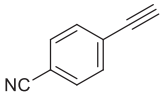
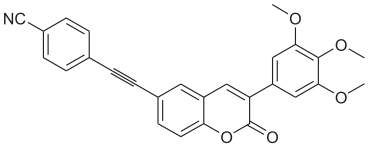
Table 3 (*continued*)

Run #	Coumarin	Aryl-ethyne	Product[a]	IL	Time[b] [h]	Yield[c] [%]
5				[BMIM][PF_6]	6	58
6				[BMIM][PF_6]	7	62
7				[BMIM][PF_6]	8	70
8				[BMIM][PF_6]	6	72
9				[BMIM][BF_4]]	8	61
10				[BMIM][BF_4]	7	64

[a] Reaction conditions: Step1**:** Aryl-acetic acid (1 mmol), CDI (1.1 mmol), [PAIM][NTf_2] (1.5 mmol), [BMIM][X] (10-12 mL), Salicylaldehyde (1 mmol), r.t., 1-2 h; Step-2: Alkyne (1.2 mmol), [PAIM][NTf_2] (1 mmol), CuI (5 mol%), $Pd(OAc)_2$ (10 mol%), 60 °C; [b]Time; [c]Isolated Yield of pure products.

work-up and product isolation, and recovery/reuse of the IL solvent (see further).

Focusing on a wider range of substituents on the salicylaldehyde, and a variety of other aryl/heteroaryl- and alkyl/cycloalkyl-substituted acetic acids, we found a number of cases where no reaction occurred at r.t. in the IL solvent by using basic-IL (Table S1), and similar observations were made when basic-IL was replaced with DBU, while raising temperature resulted in the formation unknown tarry materials. The observed trends suggest that strongly electron withdrawing substituents (e.g. NO_2, and Cl) on salicylaldehyde (as in runs 2-5 and 8; Table S1), and –SH on $PhCH_2CO_2H$ (run 10; Table S1) and bulky *ortho* substitutents (as in run 1; Table S1) should be avoided. Overall, aryl-acetic acid is superior toalkyl/cycloalkyl-acetic acid for this reaction.

Facile access to 3-(p-bromo)phenylcoumarins by this method prompted the development of an IL-mediated approach to the synthesis of novel coumarin-bearing diaryl-ethynes by the Sonogshira reaction (Table 3) in a one-pot sequential approach. Thus the 3-(p-bromo)phenylcoumarins formed by the earlier described method (Fig. 1) were subsequently allowed to react with representative arylacetylenes with $Pd(OAc)_2$ as catalyst, and CuI as additive, and the coupling products were isolated in acceptable yields. Similarly, in representative cases, 6-bromo-3-aryl-coumarins underwent Sonogashira reaction to form coupling products (Table 3). By employing this method it is possible to install highly conjugated electron-rich/electron-poor pi-decks on a coumarin platform. These types of compounds may find utility as functional materials.

Finally, focusing on the recycling/reuse of the BMIM-IL solvent, examples 11 and 18 in Table 1 were selected and they were repeated four consecutive times in [BMIM][PF_6] and in [BMIM][BF_4] solvent. The results presented in graphical format in the SI file (charts 1-2), indicate a fairly consistent trend, and in line with our findings from a previous studies,[16g,h] [BMIM][PF_6] exhibited a somewhat better recovery/reuse profile as compared to [BMIM][BF_4].

In summary, we have reported a facile IL-based one-pot method that enables the assembly of a library of 3-arylcoumarins under very mild conditions by using readily available low cost reagents. An IL-mediated one-pot sequential approach provided access to new coumarin-bearing diaryl-ethynes that may find application

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as building blocks for functional materials, and studies along those lines have been initiated in our laboratories.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.151854.

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