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Unexpected *C-N* bond formation via Smiles rearrangement: one pot synthesis of *N*-arylated coumarin/pyran derivatives

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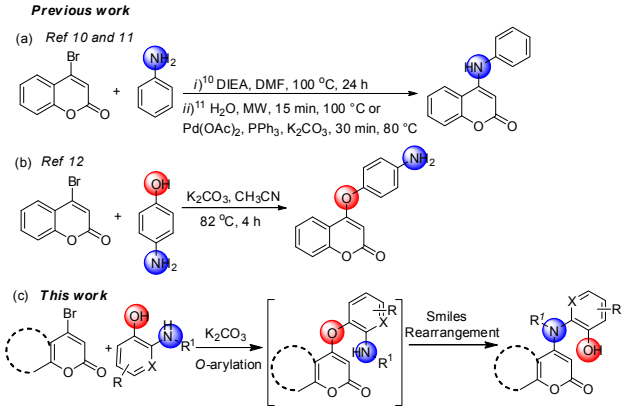
A conceptually new and one-pot method for the synthesis of *N*-arylated coumarin/pyran derivatives via smiles rearrangement. The reaction of 4-bromo coumarin/pyran reacts with 2-amino phenols to form *O*-arylated coumarin/pyran and subsequently rearrange into *N*-arylated coumarin/pyran in mild reaction conditions in good yields.

The rearrangement of C−O into C−N bond represents an interesting transformation in organic synthesis and these valuable transformations can provide access to complex natural product synthesis, heterocyclic chemistry, and industrial processes.[1] One of the interesting solution for these valuable transformations referred as Smiles rearrangement. It is an an intramolecular nucleophilic substitution in which an aromatic system shifts from one heteroatom to another *via* a spirocyclic intermediate.[2]

Smiles rearrangement are generally applicable to aromatic compounds bearing electron-withdrawing substituents.[3-5] However, heteroaryl based structures is rather limited. Funicello et al.[6] reported the three step synthesis of 4- or 5-hydroxybenzofuran rearranged to 4- or 5-aminobenzofuran under harsh reaction conditions such as NaH in DMF at 150 °C. Synthesis of *N*-alkyl/aryl-6-aminoquinolines three step one pot method by addition of 6-hydroxyquinoline and *N*-alkyl/aryl-2- chloroacetamides in the presence of Cs_2CO_3/K_2CO_3 in DMF at 150 °C was demanistrated by Shin et al.[7] Spagnolo *et al.*[8] reported that, the benzothiophene-4-ol was converted into 4-amino-benzothiophene *via* 2-methylpropionamide derivative. The rearrangement was carried out under harsh conditions using sodium hydride in HMPA or in DMF-DMPU at 100 °C. However most of these reactions are not atom economic and require harsh reaction conditions.

The coumarins framework being an integral part of many bioactive molecules is considered as one of the privileged structures in drug discovery.[9]



Scheme 1. Synthetic strategies toward the C-N bond formation on coumarin.

Reaction of 4−bromo coumarin readily reacts with anilines to provide *N*-arylated coumarins under harsh reaction conditions with long reaction time or microwave irradiation (Scheme 1a).[10-11] Where as the use of 4-amino phenols react with 4−bromo coumarin offered only *O*-arylated coumarins, there is no *N*-arylated coumarins observed (Scheme 1b)[12]. Despites of these achievements, we were interested the use of 2−aminophenols due to a challenging issue to form the either *O*-selective or *N*-selective arylated coumarins. Further, to date there have been no reports on selective synthesis of *N*-arylated coumarins and it's appeared as difficult or not feasible by using some of these methodologies.

In continuation of our interest in the developing newer and efficient methodologies for the synthesis of diverse heterocyclic scaffold,[13] we envisaged our preliminary findings on this mild, single-step, selective and metal free method for the synthesis of *N*-arylated coumarin/pyran derivatives *via* smiles rearrangement (Scheme 1c). The rearrangement of *O*-arylation into *N*-arylation of coumarin/pyran was found to be highly selective and allowed the straightforward one pot reaction from 4-bromo coumarin/pyran.

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†Electronic Supplementary Information (ESI) available: Experimental procedures, spectral data for all new compounds, and copies of spectra. CCDC 1555220. For ESI and crystallographic data in CIF and other electronic format see DOI: 10.1039/b000000x/

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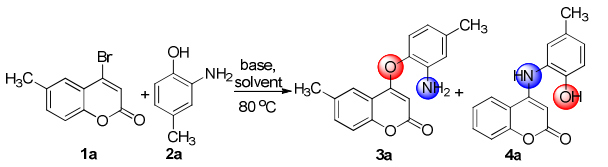
We first conduct the reaction of 4-bromo-6-methyl-2*H*-chromen-2-one **(1a)** and 2-amino-4-methylphenol (**2a**) in the presence of K_2CO_3 in DMF at 80 °C, the starting material **1a** was consumed after 6 h, To our surprise the reaction proceeded well affording 4-((2-hydroxy-5-methylphenyl)amino)-6-methyl-2*H*-chromen-2-one (**4a**) was isolated in 85% yield. However, the isolated product proved not to be the anticipated *O*-arylated coumarin. Compound **4a** was characterized by spectral (NMR, IR and HRMS) data. This motivated us to potential scope and applicability of this reaction.

We then investigated for the optimization of conditions and the results were listed in Table 1. Initially, the reaction between **1a** and **2a** in the presence of 1 equiv. of K_2CO_3, in DMF was provided only *O*–arylated chromene **3a** in good yield (Table 1, entry 1). When the reaction was carried out 2 equiv. of K_2CO_3 was employed, a mixture of *O*-arylated (**3a**, 32%) along with *N*–arylated derivative (**4a**, 55%) was obtained (entry 2) and 2.25 equiv. of K_2CO_3 was employed significantly improved *N*–arylated derivative (**4a**, 76%) (Table 1, entry 3). Interestingly, on further incresing the K_2CO_3 (2.50 equiv.), a dramatic improvement in the yield of **4a** was 85% yield (Table 1, entry 4). The further increasing the K_2CO_3 (2.75 equiv.), did not improve the yield of **4a** (Table 1, entry 5). Various bases such as Cs_2CO_3, Na_2CO_3, NaOH, NaH, and KO^{t}Bu were screened (Table 1, entries 6–10). Finally, the solvents, such as DMSO, CH_3CN, THF or Xylene (Table 1, entries 11-14) were also studied but found to be less effective then DMF (Table 1, entry 4). By lowering the reaction temperature to 60 °C led to poor substrate conversion (entry 15, Table 1). Increasing the temperature afforded the product **4a** in 80 % yield (Table 1, entry 15). Switching the inorganic base to organic base such as DBU, DABCO and TEA (Table 1, entries 17-19) decreased the product yield. Overall, it appeared that the conditions of entry 4 are optimum for obtaining the desired product **4a** in the best yield.

Table 1 Optimization of the reaction conditions.[a]

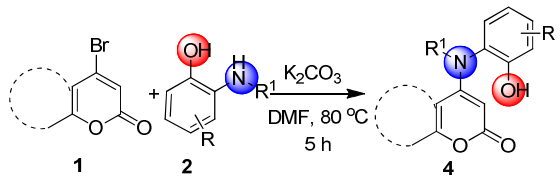


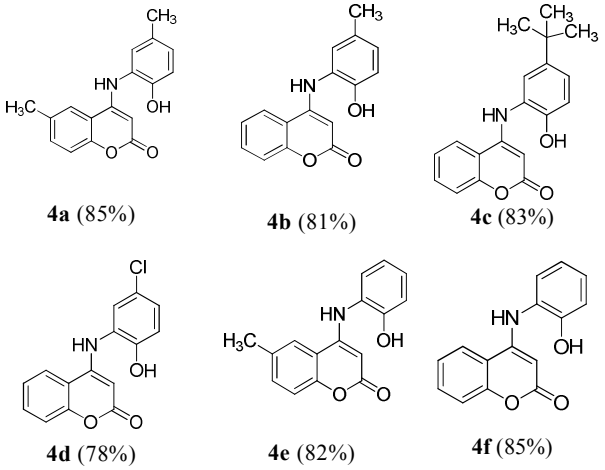
Entry	Base (equiv.)	Solvent	Time (h)	Yield (%)[b]	
				3a	4a
1	K_2CO_3 (1.25)	DMF	4	85	–
2	K_2CO_3 (2.0)	DMF	8	32	55
3	K_2CO_3 (2.25)	DMF	6	12	76
4	K_2CO_3(2.5)	DMF	5	–	85
5	K_2CO_3(2.75)	DMF	5	–	82
6	Cs_2CO_3 (2.5)	DMF	6	–	80
7	Na_2CO_3 (2.5)	DMF	8	–	75
8	NaH (2.5)	DMF	6	–	66
9	NaOH (2.5)	DMF	6	–	52
10	KO^{t}Bu (2.5)	DMF	4	–	70
11	K_2CO_3 (2.5)	DMSO	6	–	80
12	K_2CO_3 (2.5)	CH_3CN	6	–	73
13	K_2CO_3 (2.5)	THF	6	–	71
14	K_2CO_3 (2.5)	Xylene	6	–	78
15[c]	K_2CO_3 (2.5)	DMF	6	22	48
16[d]	K_2CO_3 (2.5)	DMF	5	-	80
17	DBU (2.5)	DMF	5	70	10
18	DABCO (2.5)	DMF	5	-	76
19	TEA (2.5)	DMF	5	20	45

[a]All the reactions were carried out using **1a** (0.84 m.mol), **2a** (0.84 m.mol) and base in a solvent (2 mL) at 80 °C. [b]Isolated yield. [c]The reaction was performed at 60 °C. [d]The reaction was performed at 100 °C

With the optimization conditions in hand, we decided for further investigationon the scope and generality of this present protocol. In this connection, we have conducted the reaction of a variety of 4-bromocoumarins/pyrans (**1**) with diffirent 2-aminophenols (**2**) (Table 2). As shown in Table 2, all the examined substrates provided good to high yields. The effect of electron-donating (methyl) and electron-withdrawing groups chloro) on chromen was studied and produced corresponding products (**4a, 4e, 4g–h** and **4i–l**) in good yields. The benzo[*f*]chromen also afforded the desired product with a good yield (**4n** and **4o**). To our delight, the pyran-2-one furnished the corresponding products with high yields (**4p–s and 4v**). Next, to check the feasibility of 2-aminophenol, electron-donating (methyl and *t*-butyl) (**4a-4c**, **4g**, **4j-4k**, **4q** and **4r**) and electron-withdrawing group (chloro and nitro) (**4d, 4h, 4l, 4m, 4o** and **4s**) on benzene ring, were also studied and in all of the cases it afforded the corresponding products in good yields. All the compounds characterized by spectral [IR, NMR (^{1}H and ^{13}C), and HRMS analysis.

Table 2: K_2CO_3 mediated synthesis of *N*-arylated coumarin/pyran **4**.[a,b]





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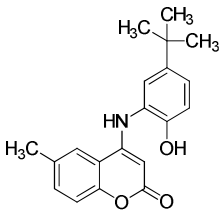
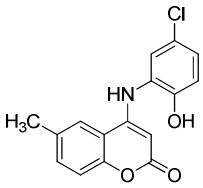
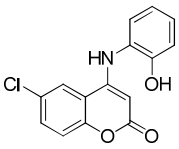
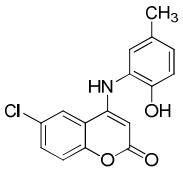
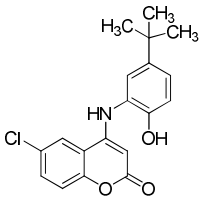
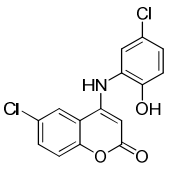

4g (82%)

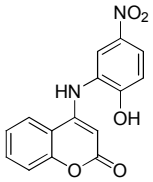

4h (75%)

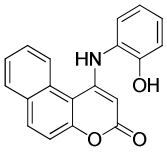

4i (85%)

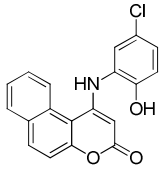

4j (86%)

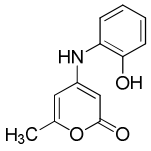

4k (80%)

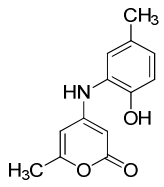

4l (85%)

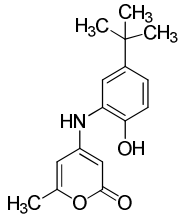

4m (81%)

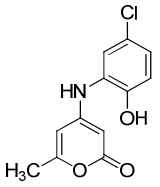

4n (80%)

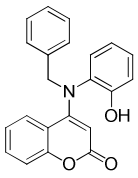

4o (76%)

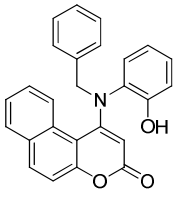

4p (80%)

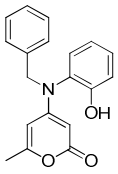

4q (81%)

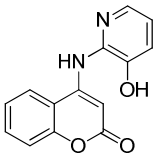

4r (86%)


4s (83%)


4t (84%)


4u (78%)

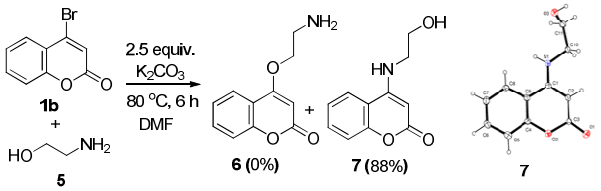

4v (80%)


4w (78%)

[a]All the reactions were carried out using compound **1a** (1.05 m. mol), **2a** (1.05 m. mol) and 2.63 m. mol. K_2CO_3 in a DMF (3 mL) at 80 °C for 5 h. [b]Isolated yield.

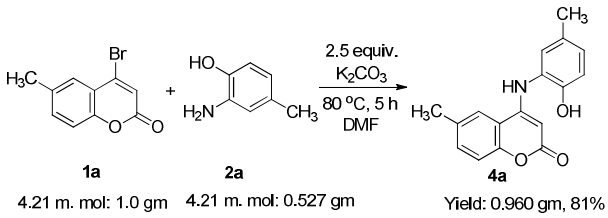
Next, we studied our present protocol with secondary *O*-aminophenol. We successfully extended C-N bond formation with secondary amines on coumarins/pyran (**4t-4v**, Table 2) with good yields (78-84%). We further extended the scope of the present protocol with pyridine derived amino phenol have also resulted in good yield of the corresponding coumarin derivative (**4w**, Table 2).

Further, we reacted **1b** with aliphatic aminol such as ethanolamine (**5**) under standard conditions and observed that the formation of *N*-alkyl coumarin (**7**), instead of the expected product **6** (Scheme 2) which was confirmed by its *X*-ray crystal analysis.[14]



Scheme 2. Reaction of **1b** with 2-aminoethanol (**5**).

In order to access the scalability of this approach, a gram scale reaction of **1a** with **2a** under optimized reaction conditions, was carried out and found yield, **4a** in 81% (0.960 g) yield (Scheme 3).



Scheme 3. Gram-Scale preparation of **4a**.

O-aryl derivative, **3a** was observed to form in 92% yields after refluxing for 3h of a mixture of **1a**, **2a** and 1.25 equiv. K_2CO_3 in DMF at 60 °C. **3a** upon further reaction with 1.25 equiv. K_2CO_3 in DMF at 80 °C for 2h, resulted in the formation of *N*-aryl derivative, **4a** in 88% yield (Scheme 4a). In order to see the comparison of the reactivity between an intermolecular and an intermolecular reaction. We carried out the reaction of 4-bromo-2*H*-chromen-2-one (**1a**) (1.0 equiv), 2-aminophenol (**2a**) (1.1 equiv), and aniline (**8**) (1.1 equiv) in DMF using 2.5 equiv of K_2CO_3 (Scheme 4b). We found that the formation of **4a** in 82% yield and *N*-aryl derivative of **8** (i.e., **9**) was not at all observed. This clearly shows that an intermolecular reaction (Smiles rearrangement) is favoured over an intermolecular reaction as aminophenol (**2a**) with an attached nucleophile is in close proximity to attack chromen carbon as compared to aniline molecule.

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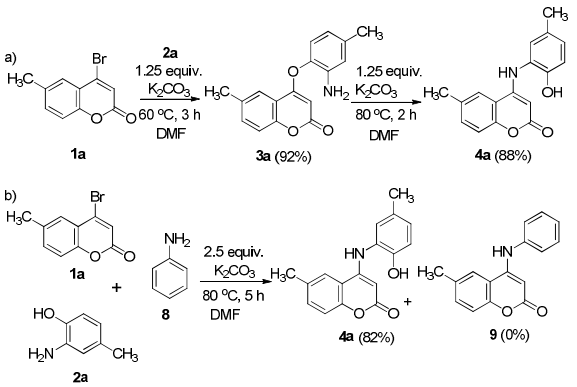
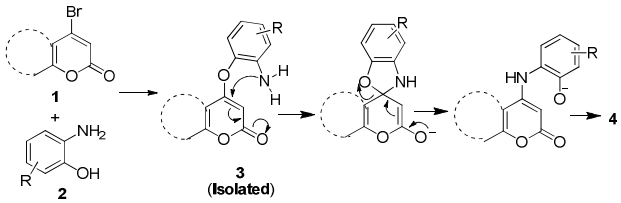


Scheme 4. Competitive study.

Based on the literature precedents[15-16] and our experimental observations, a plausible mechanism is showed in Scheme 5. Initially, *O*-aryl coumarin (**3**) formed by nucleophilic substitution participates in cyclization (*via* aza-Michael addition) results in the formation of spiro intermediate and subsequent cleavage of the weaker C−O forms a new C-N bond give to *N*-aryl coumarin/pyran **4**.



Scheme 5. Plausible mechanism**.**

In conclusion, a novel methodology has been developed via K_2CO_3 mediated C-N bond formation leading to form new coumarin/pyran derivatives via smiles rearrangement. This methodology involvesthe reaction of 4-bromo coumarin/pyran reacts with 2-amino phenols to form *O*-arylated product and subsequently rearrange into *N*-arylated product. The amount of K_2CO_3 plays important role to generate the *O*- or *N*-arylated products.The present methodology is a selective, straightforward and mild reaction conditions for synthesis of a range of *N*-arylated coumarins/pyrans.

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Conflicts of interest

The authors confirm that this article content has no conflict of interest.

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14. **Crystal data of (7):** CCDC 1825038, Single crystals suitable for X-ray diffraction of **7** DCM: EtOAc (1:1). Molecular formula = C_{11} H_{11} N_1 O_3, Formula weight = 205.21, Crystal system = Triclinic, space group = P -1, a = 8.0084(3) Å, b = 8.1626(3) Å, c = 8.5962(3) Å, V = 465.51(3) Å3, T = 296(2) K, Z = 2, Dc = 1.464 Mg/m^3, 7164 Reflections collected, 1801 [R(int) = 0.0751] independent reflections, Goodness of fit = 1.066.
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GRAPHICAL ABSTRACT

A conceptually new and one-pot method for the synthesis of *N*-arylated coumarin/pyran derivatives via smiles rearrangement.