EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201403524

Synthesis of 3-Arylisocoumarins by Using Acyl Anion Chemistry and Synthesis of Thunberginol A and Cajanolactone A

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Keywords: Natural products / Synthetic methods / Oxygen heterocycles / Alkylation / Anions / Cyclization

A new strategy for the synthesis of 3-arylisocoumarins and 8-hydroxy-3-arylisocoumarins was investigated by using acyl anion chemistry for the initial C–C bond formation. The obtained keto esters and keto lactones as intermediates underwent base-promoted intramolecular cyclization to afford 3-arylisocoumarins in good yields. The developed methodology was applied for the synthesis of the important natural products thunberginol A and cajanolactone A.

Introduction

Isocoumarins (1*H*-2-benzopyran-1-ones or 3,4-benzo-2-pyrones) are natural products that are widely available from various bioresources. Structurally, they are lactones that display a broad range of biological activities, including antibacterial activity,[1] anti-inflammatory activity,[2] antifungal activity,[3] sweetening,[4] antipheromonal effects,[5] anticancer activity,[6] and antidiabetic activity.[7] The presence of the isocoumarin scaffold in nature and the wide range of biological activities associated with it has evoked enormous interest from synthetic and medicinal chemists over the last three decades.[8] Among various substituted isocoumarins, 3-substituted isocoumarins with no substituent at the 4-position, for example, thunberginol A (**1**) and cajanolactone A (**2**, Figure 1), have remained dominant from the perspective of biological activity. Thunberginol A (**1**),[9] isolated from *Hydrangeae dulcis folium* the fermented leaves of *Hydrangea macrophylla* SERINGE var. *thunbergii* MAKINO, is a potent antiallergic agent and suppressor of T-lymphocyte proliferation,[10] whereas cajanolactone A (**2**),[11a] isolated from the leaves of *Pigeonpea* [*Cajanus cajan* (L.) Millsp], has notable hypoglycemic activity in mice and has been only recently synthesized for the first time.[11b]

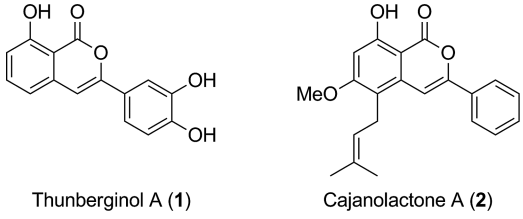

Figure 1. Pharmacologically important 3-arylisocoumarins.

Although syntheses of isocoumarins have been the subject of intense activity and despite the fact that various strategies have been developed in recent times,[12] the synthesis of 3-arylisocoumarins **3** in particular have remained confined to three main approaches. The annulation of 2-(arylethynyl)benzoic acids or the corresponding esters as substrates constitutes one of the dominant approaches. This annulation has been effected under a variety of conditions, including the use of acids such as trifluoroacetic acid (TFA),[13a] *p*-toluenesulfonic acid (*p*TsOH),[13b] CF_3SO_3H,[13c] H_2SO_4,[13d] and $FeCl_3$;[13e] halogens such as I_2[14a–14e] and Br_2;[14f] and metal complexes such as Pd/C-Ph_3P–CuI,[15a] $PdCl_2(MeCN)_2$,[15b] $Pd_2(dba)_3$ (dba = dibenzylideneacetone),[15c] $Pd(Ph_3P)_4$ $Et_3N{\cdot}ZnCl_2$,[15d] $Pd(OAc)_2$,[15e] $InBr_3$,[15f] CuI,[15g] AuCl,[15h] $Ru_3(CO)_{12}$,[15i] and Ir^{III} hydrides.[15j] Even though this approach prevails in some cases besides those with isocoumarins, isomeric 3-benzylidenephthalides eventuate as major products.[16] The oxidative cyclization of *o*-alkynylbenzaldehydes as substrates with the use of N-heterocyclic carbenes as catalysts and atmospheric oxygen as the oxidant has also been explored for the synthesis of 3-arylisocoumarins, but the reaction products always contain the isomeric alkylidene phthalides as additional products.[16e] The use of 2-halobenzoic acids or their derivatives for Cu^I-catalyzed coupling with 1,3-diketones constitutes yet another good approach for the synthesis of 3-arylisocoumarins;[17] however, substrate availability limits the versatility of this route. The use of 2-halobenzoic acids for arylation onto the activated methylene group of symmetrical β-diketones under the influence of cesium carbonate as the base has also paved way for the synthesis of 3-arylisocoumarins, but with unsymmetrical β-diketones, the reaction yields a mixture of products.[17e] The intramolecular version of the same reaction

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201403524.

with 1-(2-halophenyl)-3-arylpropane-1,3-diones has also been successful.[18] The use of 2-iodobenzoate in the palladium-catalyzed coupling with styrenes[19] and propargylic substrates[20] has also enabled the synthesis of 3-aryl- and 3-alkylisocoumarins. Well-known *ortho*-directed C–H activation by using a carboxylate group[21] has been explored for the Pd-catalyzed *ortho*-C–H coupling of benzoic acid with vinylarenes for the synthesis of 3-arylisocoumarins.[22] Although extremely attractive because it opens up avenues for both 3-arylisocoumarins and their isomeric compounds, that is, 3-benzylidenephthalides, the route is unsuitable for 3-arylisocoumarins if *ortho*-substituted benzoic acids are used.

The biological significance of 3-arylisocoumarins and the absence of a synthetic route based on simple disconnection by envisaging the use of acyl anion chemistry (Figure 2) was the rationale to undertake this study. The study has yielded a new and convenient route for the synthesis of 3-arylisocoumarins in general, and the developed route has enabled the synthesis of thunberginol A (**1**) and cajanolactone A (**2**), which are of great biological significance.

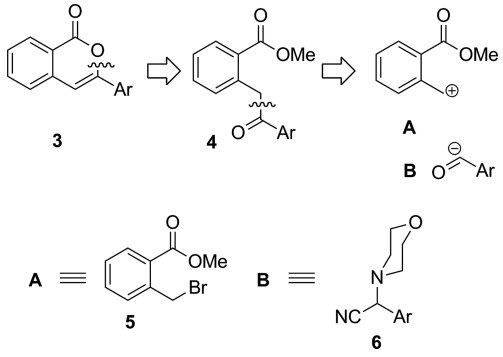
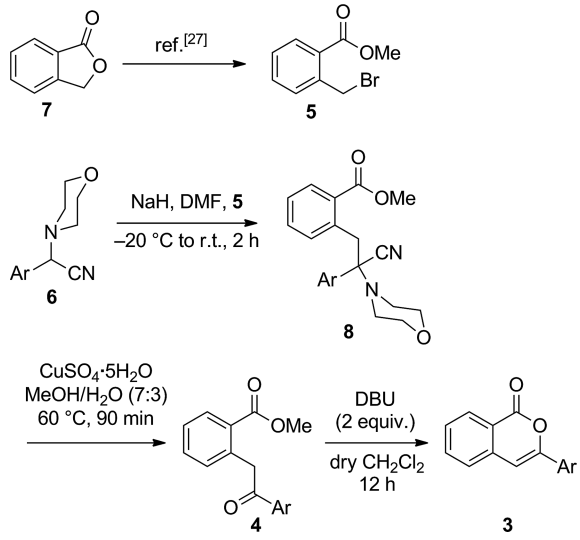


Figure 2. New disconnection for the synthesis of 3-arylisocoumarins.

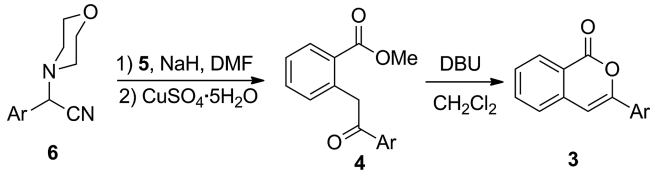
Results and Discussion

The use of α-aminonitriles **6** as arylacyl anion equivalents for synthon **B** was successfully demonstrated by us[23] and others in various synthetic endeavors.[24] The attractiveness of α-aminonitriles **6** amongst several other derivatives reported in the literature[25] is due to the simplicity and convenience of their preparation on a multigram scale.[26] Benzylic bromide **5**,[27] the requisite synthetic equivalent for electrophilic synthon **A**, was synthesized from phthalide (**7**) by using a reported procedure. α-Aminonitriles **6a**–**l** underwent clean alkylation with bromide **5** to afford corresponding alkylated intermediates **8a**–**l**. These alkylated intermediates were directly subjected to hydrolysis by using hydrated $CuSO_4$ in aqueous methanol at 60 °C.[28] Clean hydrolysis ensued to furnish desired δ-keto esters **4a**–**l** projected in the new disconnection (Scheme 1). With the obtainment of these δ-keto esters as key intermediates, proposed in the new scheme for the synthesis of 3-arylisocoumarins, successful demonstration of the use of acyl anion chemistry was achieved. Upon treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base, successful annulation occurred to afford target 3-arylisocoumarins **3a**–**l** in good yields (Scheme 1, Table 1). Debenzylation of 3-arylisocoumarins **3i**–**l** furnished corresponding free-hydroxy-containing 3-arylisocoumarins **3m**–**p** (Scheme 2).



Scheme 1. Synthesis of 3-arylisocoumarins.

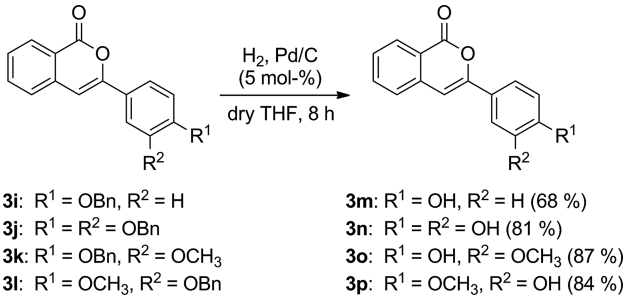
Table 1. List of 3-arylisocoumarins.



Entry	Ar, **6**	Keto ester **4** (% yield)[a]	Isocoumarin **3** (% yield)
1	Ph, **6a**	**4a** (74)	**3a** (96)
2	2-BrC_6H_4, **6b**	**4b** (65)	**3b** (87)
3	4-ClC_6H_4, **6c**	**4c** (69)	**3c** (83)
4	4-$MeOC_6H_4$, **6d**	**4d** (67)	**3d** (88)
5	3,4-$(MeO)_2C_6H_3$, **6e**	**4e** (72)	**3e** (92)
6	3,4,5-$(MeO)_3C_6H_2$, **6f**	**4f** (66)	**3f** (94)
7	3,4-$(OCH_2O)C_6H_3$, **6g**	**4g** (71)	**3g** (97)
8	2-furyl, **6h**	**4h** (69)	**3h** (82)
9	4-$BnOC_6H_4$, **6i**	**4i** (64)	**3i** (88)
10	3,4-$(BnO)_2C_6H_3$, **6j**	**4j** (72)	**3j** (86)
11	3-MeO-4-$BnOC_6H_3$, **6k**	**4k** (62)	**3k** (83)
12	3-BnO-4-$MeOC_6H_3$, **6l**	**4l** (60)	**3l** (81)

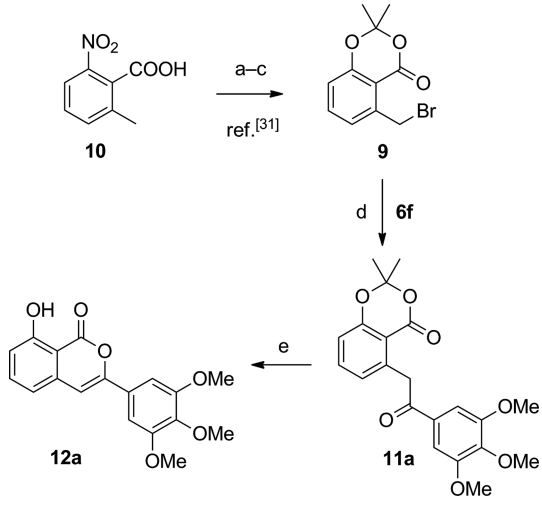
[a] Over two steps.

With the optimized reaction conditions exploiting acyl anion chemistry for the synthesis of 3-arylisocoumarins, we next aimed to synthesize 8-hydroxy-3-arylisocoumarins **12**. The hydroxy group in the 8-position of the isocoumarin framework is essential for antifungal activity[29] and for the inhibition of histamine release.[30] For the synthesis of 8-hydroxy-3-arylisocoumarins **12** through the developed synthetic route, benzylic bromide **9**[31] was conceived as the suitable equivalent for synthon **A** (in Figure 2, Scheme 3).



Scheme 2. Debenzylation of 3-arylisocoumarins.

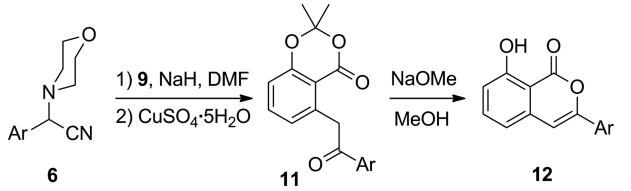
This compound was made in three steps according to the reported procedure[30] by using 2-methyl-6-nitrobenzoic acid (**10**) as the starting material. α-Aminonitrile **6f**, as a representative example (Table 1), underwent clean alkylation with benzylic bromide **9** and after hydrolysis afforded δ-keto lactone **11a** in good yield. Final cyclization to isocoumarin **12a**, however, failed to occur with DBU as the base. Presuming that unsuitable disposition of the lactone carbonyl group, probably because of the locked conformation resulting from the isopropylidene protection, could be the reason for this failure, sodium methoxide was explored as the base to effect transformation to the isocoumarin. Nucleophilic attack by methoxide on the lactone would enable in situ formation of the methyl ester, and its role as a base should facilitate the desired cyclization. To our satisfaction, successful cyclization occurred and desired isocoumarin **12a** was afforded in good yield (Scheme 3).



Scheme 3. Synthesis of 8-hydroxy-3-arylisocoumarins. Reagents and conditions: (a) 1) Pd/C, H_2, MeOH; 2) $NaNO_2$, H_2SO_4, –5 to 0 °C then 50 °C. (b) Acetone, 4-(dimethylamino)pyridine (DMAP), $SOCl_2$. (c) *N*-Bromosuccinimide (NBS), benzoyl peroxide, CCl_4. (d) 1) **6f**, NaH, dry DMF, –20 °C to r.t, 2 h; 2) $CuSO_4·5H_2O$, MeOH/H_2O (7:3), 60 °C, 90 min, 64% (2 steps). (e) NaOMe, MeOH, 6 h, 94%.

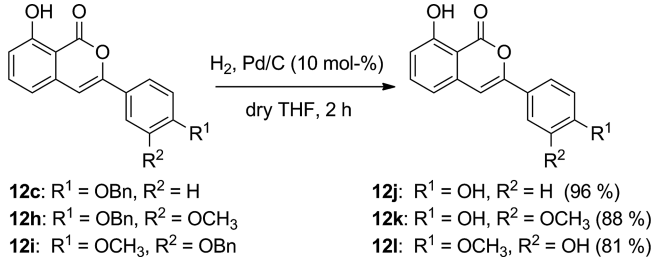
With the successful synthesis of **12a** as a representative example of 8-hydroxy-3-arylisocoumarins, the developed route was generalized and was then used for the synthesis of functionalized 8-hydroxy-3-arylisocoumarins (Table 2). Different aminonitriles substituted with electron-donating and electron-withdrawing groups were successfully treated under the determined conditions to give corresponding 8-hydroxy-3-arylisocoumarins **12b**–**i**. Simple debenzylation of **12c**, **12h**, and **12i** afforded corresponding free-hydroxy-containing 3-aryl-8-hydroxy isocoumarins **12j**, **12k**, and **12l**, respectively, in good yields (Scheme 4).

Table 2. List of 8-hydroxy-3-arylisocoumarins.



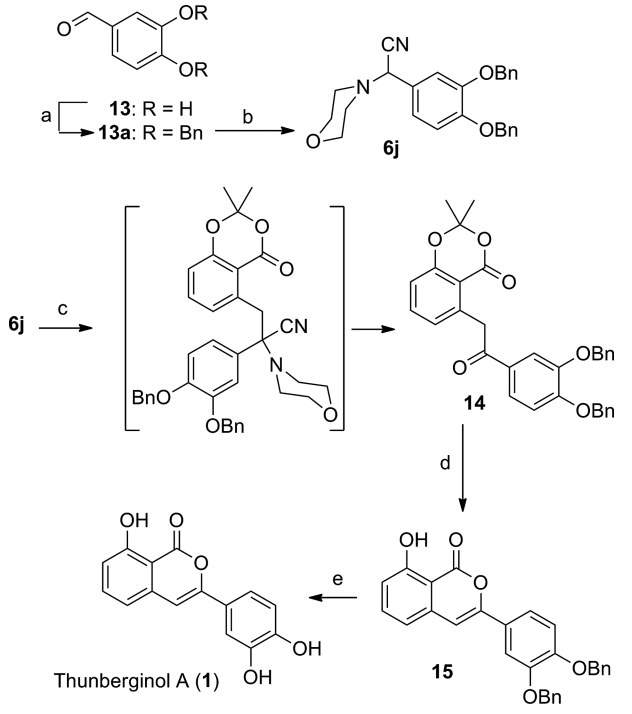
Entry	Ar, **6**	Keto lactone **11** (% yield)[a]	Isocoumarin **12** (% yield)
1	Ph, **6a**	**11b** (77)	**12b** (86)
2	4-$BnOC_6H_4$, **6i**	**11c** (67)	**12c** (88)
3	3,4-$Cl_2C_6H_3$, **6m**	**11d** (76)	**12d** (61)
4	4-FC_6H_4, **6n**	**11e** (71)	**12e** (69)
5	3-$O_2NC_6H_4$, **6o**	**11f** (60)	**12f** (61)
6	4-PhC_6H_4, **6p**	**11g** (75)	**12g** (80)
7	3-MeO-4-$BnOC_6H_3$, **6k**	**11h** (64)	**12h** (89)
8	3-BnO-4-$MeOC_6H_3$, **6l**	**11i** (61)	**12i** (67)

[a] Over two steps.

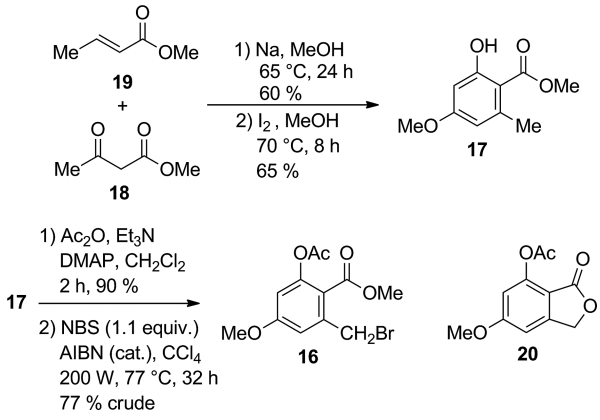


Scheme 4. Debenzylation of 8-hydroxy-3-arylisocoumarins.

With the synthesis of both 3-arylisocoumarins and 8-hydroxy-3-arylisocoumarins, the developed route was utilized for the synthesis of two important natural products, that is, thunberginol A and cajanolactone A. Although there are six reported syntheses[32] for thunberginol A, none of them use acyl anion chemistry. Hitherto unknown α-aminonitrile **6j** required for the synthesis of thunberginol A (**1**) was prepared in two simple steps and in good yield by using commercially available 3,4-dihydroxybenzaldehyde (**13**) as the starting material (Scheme 5). α-Aminonitrile **6j** underwent clean alkylation with benzylic bromide **9** and after hydrolysis afforded δ-keto lactone **14**. Upon treatment with sodium methoxide, δ-keto lactone **14** afforded isocoumarin **15**, which upon debenzylation gave natural thunberginol A (**1**, Scheme 5).



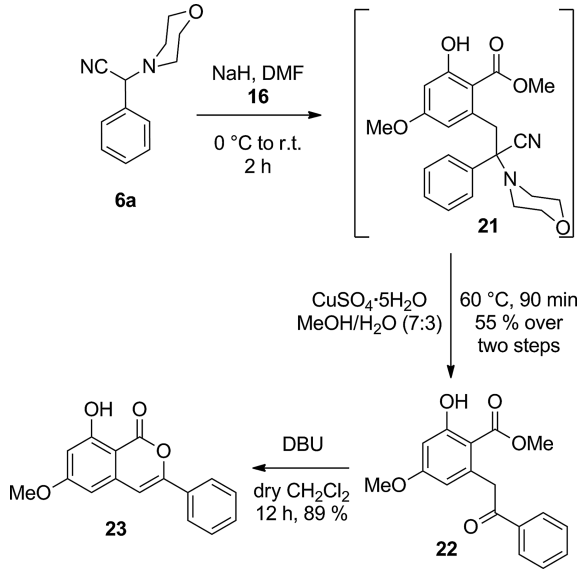
Scheme 5. Synthesis of thunberginol A (**1**). Reagents and conditions: (a) $PhCH_2Br$, K_2CO_3, acetone, reflux, 6 h, 86%. (b) Morpholine, NaCN, $NaHSO_3$, H_2O, 13 h, 75%. (c) 1) **6j**, NaH, dry DMF, **9**, –20 °C to r.t, 2 h; 2) $CuSO_4{\cdot}5H_2O$, MeOH/H_2O (7:3), 60 °C, 90 min, 72% (2 steps). (d) NaOMe, MeOH, 6 h, 94%. (e) H_2, Pd/C, anhydrous THF, 2 h, 92%.



Scheme 6. Synthesis of bromide **16**; AIBN = 2,2′-azobisisobutyronitrile.

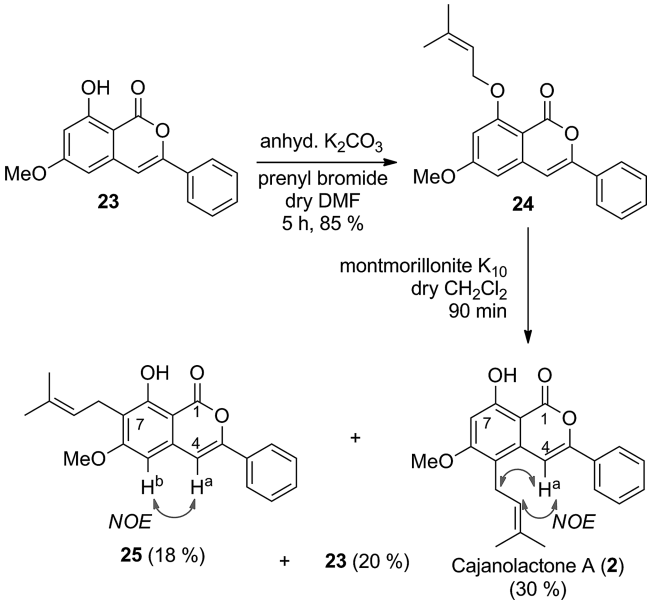
For the synthesis of the second natural product cajanolactone A (**2**), functionalized benzyl bromide **16** was synthesized in two steps from orsellinic acid derivative **17** as the starting point. The limited availability of **17** from nature has been addressed through an alternative synthetic approach[33] involving base-catalyzed condensation of commercially available methyl acetoacetate (**18**) and methyl crotonate (**19**) in dry methanol followed by aromatization by using I_2/MeOH. Compound **17** was subjected to acetylation by using acetic anhydride and triethylamine as the base in CH_2Cl_2 followed by benzylic bromination with *N*-bromosuccinimide in refluxing CCl_4 under 200 W light to give corresponding bromide **16** (Scheme 6). Although bromide **16** has been isolated in high yield for the bromination step,[34] in our hands compound **16** was not stable and easily cyclized to phthalide **20**. Also, in the bromination step the starting material was not completely consumed, even after 32 h, and beyond this time, already-formed bromide **16** cyclized to undesired phthalide **20** (Scheme 6).

Purification was done by using a fast filtration column to remove the phthalide, and bromide **16** containing unreacted starting material (which is not separable by column chromatography) was directly used for the alkylation reaction in the subsequent step. α-Aminonitrile **6a** underwent alkylation with bromide **16** by using sodium hydride as the base in dry DMF with concomitant deprotection of the acetyl group during aqueous workup. Acidic hydrolysis of alkylated intermediate **21** gave ketone **22** in 55% yield over two steps. Aryl ketone **22** underwent clean cyclization with DBU as the base to furnish 8-hydroxy-6-methoxy-3-arylisocoumarin **23** (Scheme 7). The phenolic hydroxy group in **23** was alkylated with prenyl bromide by using potassium carbonate as the base. *O*-Prenyl ether derivative **24** obtained in 85% yield was subjected to rearrangement by using montmorillonite K10 in dichloromethane. The rearrangement resulted in the formation of two isomeric compounds, besides deprenylated compound **23** (20%, Scheme 8). NMR spectroscopy studies on the major isomer (30%, R_f = 0.44, EtOAc/hexanes = 1:4) revealed that it was the desired cajanolactone A (**2**). The signals at δ = 6.52 and 7.03 ppm in the ^{1}H NMR spectrum for the major compound were assigned to the protons attached to C7 and C4, respectively. This was supported through their correlation with ^{13}C NMR signals at δ = 98.35 and 100.19 ppm in the HSQC spectrum. Final confirmation of this assignment came through the 2D NOESY spectrum, which showed two correlations for the C4 proton signal at δ = 7.03 ppm. The first correlation was for the allylic methylene protons sig-



Scheme 7. Synthesis of isocoumarin **23**.

nals (doublet at δ = 3.45 ppm) and the second correlation was for the vinylic proton signal (multiplet at δ = 5.06 ppm) of the prenyl group. These two correlations clearly showed the closer proximity of the prenyl group to the C4 proton and hence confirmed the major isolated product as the targeted cajanolactone A (**2**). As expected, the NOESY spectrum for the minor component (18%, R_f = 0.41, EtOAc/hexanes = 1:4) had no correlation between the C4 proton signal (singlet at δ = 6.88 ppm) and the prenyl group. It instead showed correlation with a signal at δ = 6.45 ppm (singlet) corresponding to the C5 aromatic proton. The melting point of the major isomer is 125–127 °C, which is in good agreement with the literature-reported value[11b] (127–129 °C), whereas the melting point of the *ortho* isomer, synthesized for the first time, is 152–154 °C. The obtainment of easily separable isomers **2** and **25** is advantageous from the perspective of biological studies, as a single reaction affords both compounds. The formation of deprenylated **23** is also not disadvantageous, as it can be subject to the same cycle, **23**→**24**→**2**/**25**, which precludes any waste of precious material.



Scheme 8. Synthesis of cajanolactone A (**2**).

Conclusions

In conclusion, we successfully developed a convenient route for the synthesis of 3-arylisocoumarins and 8-hydroxy-3-arylisocoumarins by using acyl anion chemistry. The route enabled the synthesis of the important natural products thunberginol A and cajanolactone A. The developed route makes use of readily available starting materials and simple reaction procedures.

Experimental Section

General Information: All reactions were performed in oven-dried glassware. Reactions requiring an inert atmosphere were performed under a nitrogen atmosphere. Dry DMF was prepared by stirring with calcium hydride and was stored over 4 Å molecular sieves after downward distillation. Solvents used for chromatography were LR grade. All reactions were monitored by TLC on precoated silica gel Merck F_{254} plates. The solvent system used throughout, unless otherwise specified, was EtOAc/hexane with various percentage of polarity depending on the nature of the substrate. Spot detection on TLC was done by exposure of the plate to UV radiation at both 235 and 350 nm. Melting points were determined in capillaries. ^{1}H NMR (400 and 500 MHz) and ^{13}C NMR (100 and 125 MHz) spectra were recorded with $CDCl_3$ or [D_6]DMSO as the solvent and tetramethylsilane as the reference. Mass spectra were recorded with a Micro-Q TOF mass spectrometer by using the ESI technique at 10 eV. IR spectra were recorded with a Jasco-FTIR-4100 spectrometer. Elemental analysis was determined by using a Perkin–Elmer Instruments series II CHNS/O analyzer. Starting α-aminonitriles **6a–l** were prepared by using a literature-known protocol[26] and were fully characterized before use.

General Procedure for Alkylation of α-Aryl Aminonitriles and Preparation of Aryl Ketones 4a–l, 11a–i, 14, and 22 (Procedure A): A solution of α-aryl aminonitrile **6a–l** (1.1 equiv.) in DMF (10 mL) was added to a suspension of NaH (1.2 equiv.) in DMF (10 mL) at –20 °C under an inert atmosphere. After 20 min, a solution of the requisite bromide (**5** for **4a–l**, **9** for **11a–i**, **14** and **16** for **22**; 1 equiv.) in DMF (20 mL) was added to the mixture, which was stirred for 2 h at room temperature. Upon completion of the reaction (TLC monitored), a saturated solution of NH_4Cl (15 mL) was added, and the organics were extracted with EtOAc (3× 20 mL). The combined organic layer was washed with water (3× 20 mL) and dried with Na_2SO_4. Removal of the solvent under reduced pressure afforded the alkylated compound. Without further purification, a solution of $CuSO_4$·$5H_2O$ (5 equiv.) in CH_3OH/H_2O (7:3, 15 mL/g of alkylated compound) was added, and the mixture was heated at reflux at 60 °C for 90 min. The solvent was evaporated under reduced pressure. Water (10 mL) was added to the obtained residue. The aqueous layer was extracted with EtOAc (3× 20 mL). Then, the combined organic layer was washed with a saturated solution of $NaHSO_3$ (3× 15 mL) and brine (10 mL) and was finally dried with Na_2SO_4. The solvent was evaporated, and the obtained residue was purified by silica gel column chromatography (EtOAc/hexanes = 1:4) to yield the corresponding aryl ketone.

General Procedure for the Synthesis of 3-Arylisocoumarins 3a–l and 23: DBU (2 equiv.) was added by micropipette under an inert atmosphere to a solution of the aryl ketone (**4a–l** for **3a–l**, **22** for **23**; 1 equiv.) in dry CH_2Cl_2 (4 mL). The mixture was stirred for 12 h. Then, CH_2Cl_2 (20 mL) was added to the mixture. The mixture was washed with 20% HCl (4× 20 mL). After that, the organic layer was washed with water (20 mL) and finally dried with Na_2SO_4. The organic layer was concentrated under reduced pressure, and the residue obtained was purified by column chromatography over silica gel (EtOAc/hexanes = 1:9) to yield the corresponding 3-arylisocoumarins.

General Procedure for the Synthesis of 8-Hydroxy-3-arylisocoumarins 12a–i and 15: NaOMe (1.1 equiv.) was added under inert atmosphere to a solution of the aryl ketone (**11a–i** for **12a–i**, **14** for **15**; 1 equiv.) in dry methanol (3 mL). The mixture was stirred for 6 h under an inert atmosphere at room temperature. Then, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography to obtain the corresponding 8-hydroxy-3-arylisocoumarin.

Synthesis of Thunberginol A (1): 10% Pd/C (10 mol-%) was added to a solution of isocoumarin **15** (0.100 g, 0.22 mmol) in THF

(3 mL), and the mixture was stirred for 2 h under a hydrogen atmosphere at room temperature. After stirring, the solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography to obtain the desired product as a pale yellow solid, yield 92% (0.055 g). R_f = 0.41 (EtOAc/hexanes = 2:3), m.p. 243–245 °C (ref.[13c] 241–244 °C). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 6.86 (d, J = 8.0 Hz, 1 H), 6.91 (d, J = 8.0 Hz, 1 H), 7.21–7.23 (m, 2 H), 7.28 (s, 1 H), 7.08 (d, J = 7.5 Hz, 1 H), 7.67 (t, J = 7.5 Hz, 1 H), 9.34 (s, 1 H, OH), 9.61 (s, 1 H, OH), 10.84 (s, 1 H, OH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 100.7, 105.3, 112.3, 114.1, 116.1, 116.7, 117.1, 122.4, 137.7, 138.6, 145.7, 147.9, 152.8, 160.5, 165.3 ppm. IR (KBr): $\tilde{\nu}$ = 2980, 2851, 1669, 1612, 1525, 1172 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{10}O_5Na$ [M + Na]$^+$ 293.0426; found 293.0420.

Synthesis of *O*-Prenyl Ether 24: Under a nitrogen atmosphere, anhydrous K_2CO_3 (0.495 g, 3.58 mmol) and prenyl bromide (0.12 mL, 1.07 mmol) were added to a stirred solution of isocoumarin **23** (0.240 g, 0.89 mmol) in dry DMF (8 mL). After 5 h, the mixture was diluted with water (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with water (3 × 20 mL) and brine (15 mL) and was finally dried with Na_2SO_4. The solvent was evaporated, and the obtained residue was purified by silica gel column chromatography (EtOAc/hexanes = 1:4) to yield title compound **24**, yield 85% (0.255 g). R_f = 0.54 (EtOAc/hexanes = 1:4). Colorless solid, m.p. 117–119 °C (ref.[11b] 123–124 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.77 (s, 3 H, OCH_3), 1.79 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 4.70 (d, J = 6.3 Hz, 2 H), 5.55–5.59 (m, 1 H), 6.45 (s, 2 H), 6.76 (s, 1 H), 7.40–7.44 (m, 3 H), 7.84–7.87 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.5, 25.9, 55.7, 66.5, 100.2, 100.6, 102.0, 103.9, 119.4, 125.4, 128.8, 130.0, 132.1, 137.9, 142.2, 154.3, 158.7, 162.7, 165.3 ppm. IR (KBr): $\tilde{\nu}$ = 3022, 2926, 1591, 1424, 1213 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{20}O_4Na$ [M + Na]$^+$ 359.1259; found 359.1252.

Synthesis of Cajanolactone A (2): Montmorillonite K_{10} (0.300 g) was added to a solution of *O*-prenyl ether **24** (0.100 g, 0.29 mmol) in dry CH_2Cl_2 (4 mL) at 0 °C. The mixture was stirred for 1.5 h at room temperature. After this, the mixture was filtered through a pad of Celite, and the residue was washed with CH_2Cl_2. The solvent was evaporated, and the obtained residue was purified by silica gel column chromatography (EtOAc/hexanes = 1:4) to yield title compound **2** (30%), along with **25** (18%) and **23** (20%). Data for **2**: Yield: 30% (0.030 g). R_f = 0.44 (EtOAc/hexanes = 1:4). Colorless solid, m.p. 125–127 °C (ref.[11b] 127–129 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.69 (s, 3 H, CH_3), 1.85 (s, 3 H, CH_3), 3.45 (d, J = 6.8 Hz, 2 H, allylic CH_2 of prenyl group), 3.89 (s, 3 H, OCH_3), 5.05–5.09 (m, 1 H, vinylic CH of prenyl group), 6.52 (s, 1 H, C7-H), 7.03 (s, 1 H, C4-H), 7.42–7.49 (m, 3 H), 7.81–7.85 (m, 2 H), 11.29 (s, 1 H, OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.1, 23.7, 25.8, 56.0, 98.3, 99.7, 100.1, 116.1, 122.7, 125.3, 129.0, 130.1, 132.0, 132.1, 136.1, 152.6, 162.6, 164.4, 166.5 ppm. IR (KBr): $\tilde{\nu}$ = 3684, 3025, 2926, 2854, 1516 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{21}O_4$ [M + H]$^+$ 337.1440; found 337.1433. Data for **25**: Yield: 18% (0.018 g). R_f = 0.41 (EtOAc/hexanes = 1:4). Colorless solid, m.p. 152–154 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.68 (s, 3 H, CH_3), 1.80 (s, 3 H, CH_3), 3.40 (d, J = 7.0 Hz, 2 H, allylic CH_2 of prenyl group), 3.93 (s, 3 H, OCH_3), 5.19–5.24 (m, 1 H, Vinylic CH of prenyl group), 6.45 (s, 1 H, C5-H), 6.88 (s, 1 H, C4-H), 7.43–7.47 (m, 3 H), 7.83 (d, J = 7.8 Hz, 2 H), 11.22 (s, 1 H, OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.9, 22.2, 25.9, 56.0, 98.3, 100.5, 103.1, 116.9, 121.6, 125.2, 128.9, 130.0, 131.7, 132.3, 137.2, 152.8, 160.0, 164.4, 166.2 ppm. IR (KBr): $\tilde{\nu}$ = 3684, 3025, 2926, 2854, 1516 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{21}O_4$ [M + H]$^+$ 337.1440; found 337.1429.

Supporting Information (see footnote on the first page of this article): Experimental details and copies of the ^{1}H NMR, ^{13}C NMR, and HRMS spectra of all new compounds.

Acknowledgments

The authors thank the Department of Science and Technology (DST), New Delhi, for funding towards the 400 MHz NMR spectrometer to the Department of Chemistry, Indian Institute of Technology Madras (IIT-Madras), under the Intensification of Research in High Priority Areas (IRPHA) Scheme and the ESI-MS facility under the Fund for Improvement of Science & Technology Infrastructure (FIST) program. The Board of Research in Nuclear Sciences (BRNS) is acknowledged for funding of project-2013. K. S. acknowledges the University Grants Commission (UGC), New Delhi for a Senior Research Fellowship.

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Received: November 25, 2014
Published Online: ■

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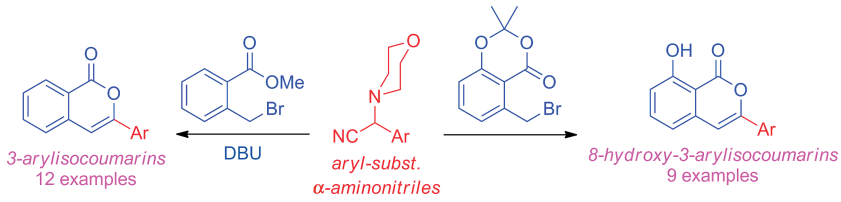

3-Arylisocoumarins are synthesized by using a new strategy based on acyl anion chemistry. Aryl-substituted α-aminonitriles are used as acyl anion equivalents in this study. Further, the route is general and can be applied to the synthesis of 8-hydroxy-3-arylisocoumarins, including thunberginol A and cajanolactone A, which are naturally occurring isocoumarins known for their biological activities. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Keywords: Natural products / Synthetic methods / Oxygen heterocycles / Alkylation / Anions / Cyclization

