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Simple and Efficient Copper(I)-Catalyzed Access to Three Versatile Aminocoumarin-Based Scaffolds using Isocyanoacetate

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Abstract: An efficient method has been developed for the one-pot copper(I)-catalyzed synthesis of 3-aminocoumarin and its derivatives, such as 3-substituted methylideneaminocoumarins and chromeno-[3,4-*d*]imidazol-4(1*H*)-ones. Significantly, the strategy presents a straightforward and efficient approach to constructing biologically useful molecular scaffolds.

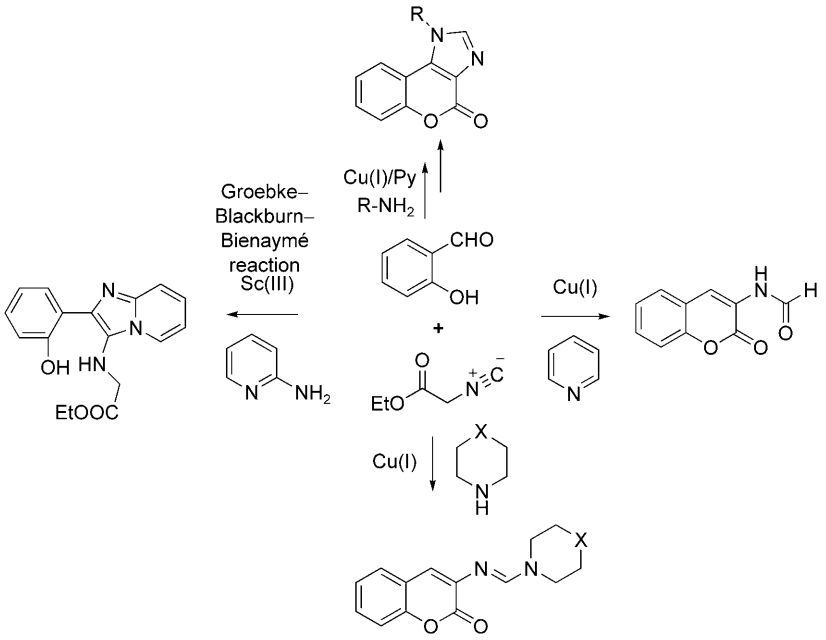
Keywords: 3-aminocoumarin; chromeno[3,4-*d*]imidazol-4(1*H*)-ones; copper(I)-catalyzed heterocycle formation; ethyl isocyanoacetate; 3-substituted methylidene-aminocoumarins

During the last decades, the study of the biological activities of coumarin derivatives has been the aim of many researchers. Coumarin and its derivatives occur widely in medicinal chemistry, and are considered to be "privileged structures" in the pharmaceutical and agrochemical industries.[1] A particularly interesting group of coumarins is 3-aminocoumarins, since they are used as CNS depressant,[2] antitumor,[3] anti-inflammatory,[4] and antimicrobial agents.[5] In addition, these compounds are also known to exhibit interesting photochemical behavior and have been used as fluorescent markers.[6] 3-Aminocoumarins are generally prepared by utilizing the corresponding salicylaldehydes and *N*-acetylglycine, and has been conducted in acidic media and at high temperatures, with low yields and tedious work-up procedures.[7] Thus, new and efficient methods to prepare 3-aminocoumarins using readily available starting materials under mild reaction conditions are strongly desired. Herein, we wish to disclose a new procedure for the efficient synthesis of this pharmaceutically useful scaffold and its derivatives.

Multicomponent reactions (MCRs) are a powerful tool in the modern drug discovery process in terms of lead finding and lead optimization, and has gained considerable and steadily increasing academic, economic and ecological interest.[8] As part of our ongoing efforts to prepare novel fused imidazole ring systems,[9,10] which are of great interest to the pharmaceutical industry, we recently focused on the Groebke–Blackburn–Bienaymé multicomponent reaction or GBB-MCR (Scheme 1).[11] It involves the reaction of 2-aminopyridine, salicylaldehyde and ethyl isocyanoacetate, and is catalyzed by scandium triflate to afford 3-aminoimidazo[1,2-*a*]pyridines in good yields (>80%). However, we accidentally found that by using $Cu(OTf)_2$ as catalyst in this reaction, one strong fluorescent spot was observed in thin layer chromatography (TLC) analysis. Single crystal X-ray diffraction analysis then showed this compound to be 3-formamidocoumarin (Figure 1), obtained in 33% yield (entry 1, Table 1).

These results prompted us to turn our attention to optimizing the conditions for the efficient formation of 3-formamidocoumarins, which then could be easily deprotected under acidic conditions to afford the pharmaceutically useful 3-aminocoumarin intermediates.

Initially, we chose salicylaldehyde and ethyl isocyanoacetate as the model substrates to optimize the reaction conditions. After testing various solvents, methanol was selected to be used in the reaction because of its ability to dissolve the starting materials but not the products, which precipitated upon reaction completion and could be easily isolated by filtration. Thus, the preliminary investigation (Table 1) was carried out in methanol at 40–50 °C for 5 h. No de-



Scheme 1. General three-component condensation reaction.

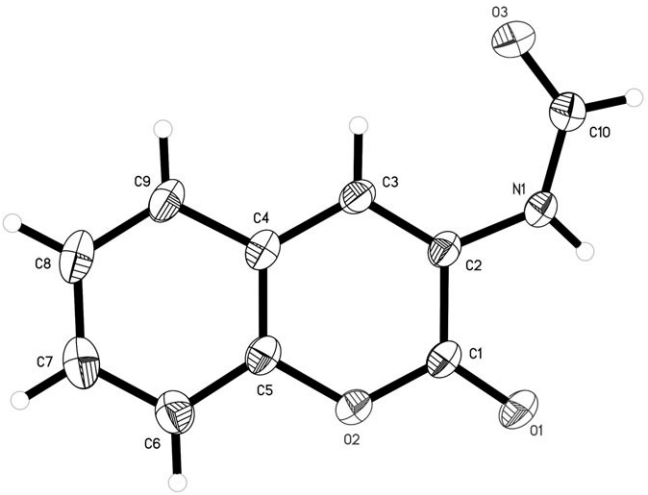


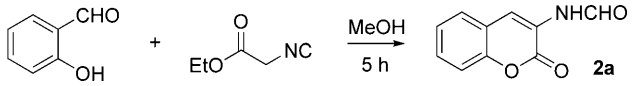
Figure 1. X-ray crystal structure of **2a**.[12]

sired product was observed in the absence of either a copper source (entries 2 and 10) or 2-aminopyridine (entry 3). While by replacing 2-aminopyridine with aniline or pyridine, only pyridine led to the formation of the desired product in 35% yield (entry 5). The nature of the base was found to have a pronounced impact on the process. Pyridine and DMAP were shown to be more effective than DBU and DIPEA (entries 6–8). Among the different copper salts tested, CuI was the best catalyst for this reaction, and the corresponding yield was enhanced up to 81% (entries 9, 11 and 12).

It is interesting to note, that under the optimized conditions (CuI, pyridine, MeOH, 50 °C) salicylaldehyde and ethyl isocyanoacetate in the presence of a secondary amine such as piperidine undergo a three-component reaction leading to 3-methylideneaminocoumarins (**4a–c**). Whereas, in the presence of a primary amine, the reaction affords an imidzole ring instead of a coumarin, which can then be converted to a chromeno[3,4-*d*]imidazol-4(1*H*)-one under microwave heating conditions using potassium carbonate as the base (Scheme 2). The structures of both three-component condensation (3CC) products were confirmed by single-crystal X-ray analysis of representative compounds **4b** and **5a** (Figure 2).

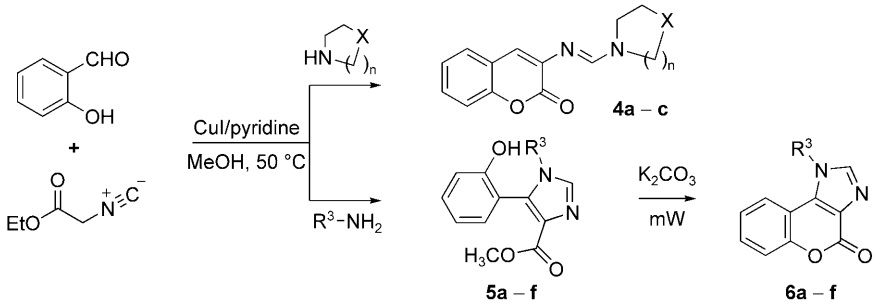
To gain insight into the reaction mechanism, we performed a labeling study with deuterated solvent. The reaction of ethyl isocyanoacetate in the presence of CuI/pyridine in CD_3OD led to the bideuteration of the α-position (see Supporting Information for full details of *ee* determination), which suggests the presence of intermediate **A** (Scheme 3). On the basis of this observation, we propose that a possible mechanism of the reaction may proceed *via* the initial formation of the activated Cu(I)-isocyanide complex,[13] which is deprotonated by pyridine to form **A**, which then attacks the salicylaldehyde to give aldol adduct **B**. Subsequent intramolecular rearrangement (**B**→**E**) and 5-*endo-dig* ring closure (**E**→**F**) generate the 3-formamidocoumarin product **G**. If carried out in the presence of a secondary amine (e.g., piperidine), intermediate **E** is attacked nucleophilically by piperidine to form **H**, followed by intramolecular rearrangement to give a 3-substituted methylideneaminocoumarin (**I**) as the product. In the presence of a primary amine, initial condensation with the salicylaldehyde

Table 1. Reaction conditions.



Entry	Conditions	Yield [%]
1	2-aminopyridine (1.0 equiv.), $Cu(OTf)_2$ (0.1 equiv.), 50 °C	33[a]
2	2-aminopyridine (1.0 equiv.), 50 °C	0
3	$Cu(OTf)_2$ (0.1 equiv.), 50 °C	0
4	aniline (1.0 equiv.), $Cu(OTf)_2$ (0.1 equiv.), 50 °C	0
5	Pyridine (1.0 equiv.), $Cu(OTf)_2$ (0.1 equiv.), 50 °C	35[a]
6	DMAP (1.0 equiv.), $Cu(OTf)_2$ (0.1 equiv.), 40 °C	30[a]
7	DBU (1.0 equiv.), $Cu(OTf)_2$ (0.1 equiv.), 40 °C	trace
8	DIPEA (1.0 equiv.), $Cu(OTf)_2$ (0.1 equiv.), 40 °C	trace
9	pyridine (1.0 equiv.), $CuCl_2$ (0.1 equiv.), 50 °C	18[a]
10	pyridine (1.0 equiv.), $FeCl_3$ (0.1 equiv.), 50 °C	0
11	pyridine (1.0 equiv.), $Cu(OAc)_2$ (0.1 equiv.), 50 °C	25[a]
12	pyridine (1.0 equiv.), CuI (0.1 equiv.), 50 °C	81[b]

[a] Yield [%] of isolated product after column chromatography.
[b] Yield of crystalline compound isolated by filtration (no recovery from mother liquor), hence the total yield may be higher.



Scheme 2. Multicomponent synthesis of 3-substituted methylideneaminocoumarins and chromeno[3,4-*d*]imidazol-4(1*H*)-ones.

forms an imine (**J**) which is then attacked by **A** to form intermediate **K**. Subsequent 5-*endo-dig* ring closure and protonation form the imidazoline **L**. The latter is rapidly oxidized to imidazole **M**.

With the identification of the optimal reaction conditions, we wished to extend the utility of the reaction. As shown in Table 2, seven commercially available substituted salicylaldehydes (**1a–g**, entries 1–7), two 2′-hydroxyacetophenones (**1h** and **i**, entries 8 and 9), and 2′-hydroxypropiophenone (**1j**, entry 10) bearing electron-withdrawing and electron-donating substituents were selected. The simplicity of a one-pot procedure is perfectly amenable to automation for combinatorial synthesis. Likewise, all the syntheses were performed on a 12-reaction set-up in a parallel synthesizer (Radleys Discovery Technology, Carousel 12 Place Reaction Station) to give the key 3-formamidocoumarin intermediates **2a–j** (Table 2). According to Table 1, the reaction rate appeared to be sensitive to steric effects: reactions with larger R^2 groups required longer times for completion (entries 8–10). Finally, removal of the formyl group using 5 equivalents of concentrated HCl in methanol afforded the pure 3-aminocoumarins (**3a–j**) in excellent yields.

In Table 3, pyrrolidine, piperidine, and morpholine were selected as the substrates in the 3CC reaction, to afford the 3-substituted methylideneaminocoumarins (**4a–c**, Table 3) in moderate yields. Meanwhile, various primary amines were used in the construction of imidazole derivatives (**5a–f**). The reaction was found to proceed with a range of R^3 groups, including aliphatic groups and aromatic rings. Subsequent ring-closing reaction furnished the polycyclic products **6a–f** in moderate overall yields. Notably, such benzopyranimidazolones were revealed as PDE7 inhibitors, but no synthetic method was disclosed.[14]

In summary, by using ethyl isocyanoacetate as a glycine equivalent, an efficient avenue for the facile and atom-economic synthesis of two types of 3-aminocoumarin derivatives under mild conditions was developed. Furthermore, the same conditions can be used to generate *N*-substituted chromeno[3,4-*d*]imi-

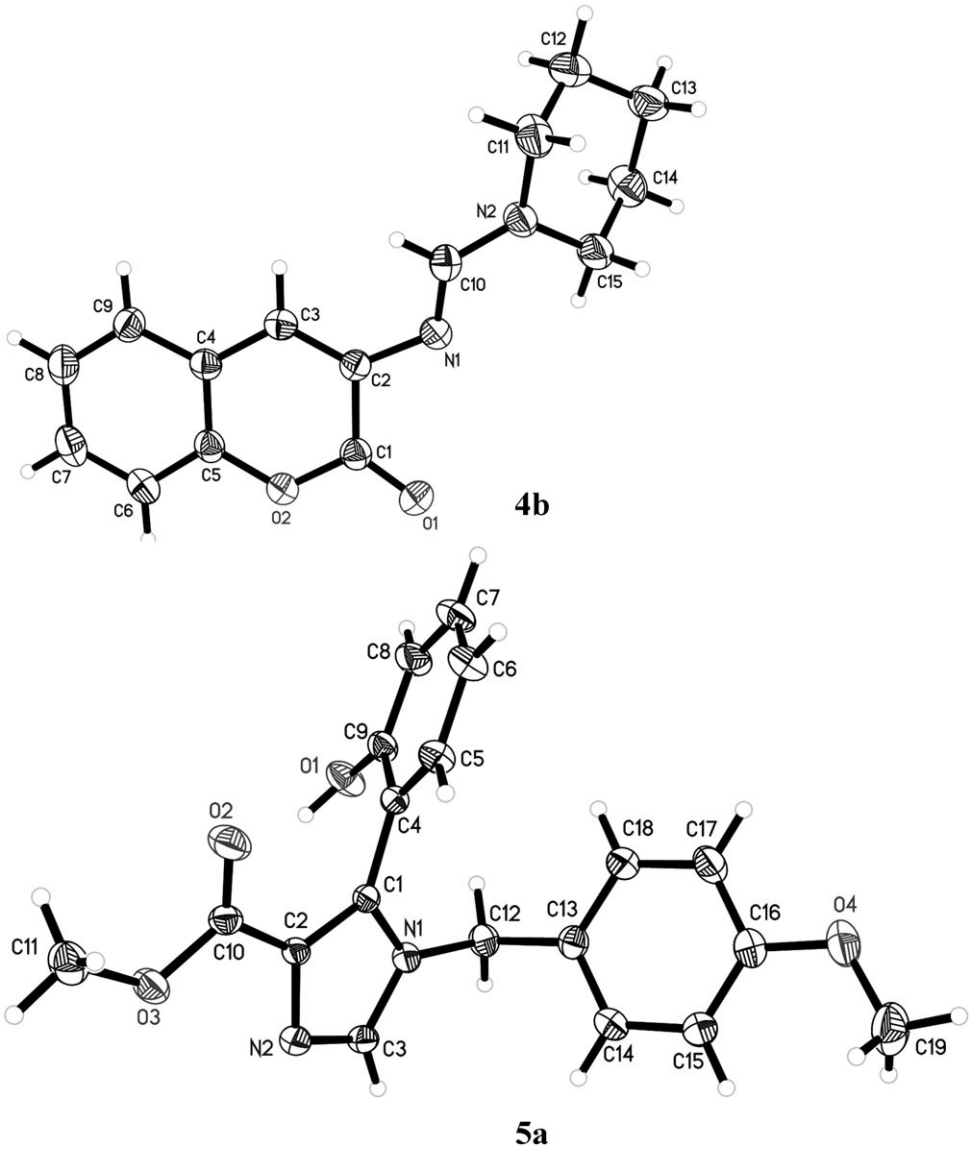
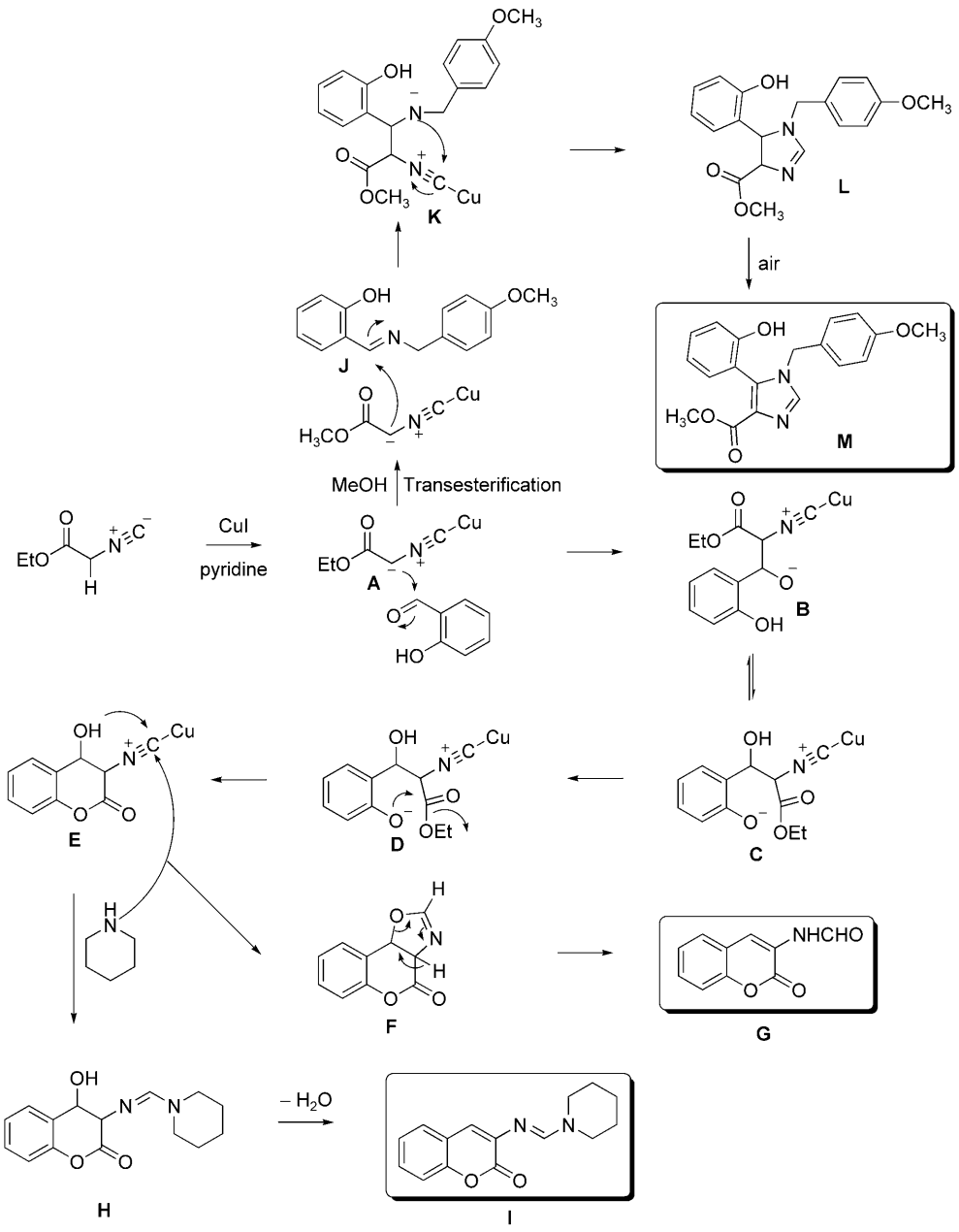


Figure 2. X-ray crystal structures of **4b** and **5a**.[12]

dazol-4(1*H*)-ones. The protocol uses readily available starting materials, and the corresponding target products are obtained in moderate to high yields. The copper catalyst used was active without additional coordinating ligands. 3-Aminocoumarins are well-known as biologically and pharmaceutically active molecules, as well as chromophores of many fluorescent proteins, therefore, the present method will be of wide application in organic and medicinal chemistry.

Experimental Section

The ^{1}H NMR (300 MHz) spectra were recorded using Varian Mercury-300 High Performance Digital FT-NMR with TMS as internal standard, and the ^{13}C NMR (100 MHz) spectra were recorded using Varian Mercury-400 High Performance Digital FT-NMR. The LC-MS were carried out on Thermo Finnigan LCQDECAXP and low-resolution EI-MS was measured on a MAT-95 spectrometer and HR-EI-MS on a MAT-77 spectrometer. Purity was recorded on Gilson high-performance liquid chromatography (HPLC) (306 pump, UV/vis-156 Detector, 215 liquid handle). TLC was carried out with glass pre-coated silica gel GF_{254} plates. TLC spots were visualized under UV light. All the solvents and reagents were used directly as obtained commercially unless otherwise noted. A Biotage Initiator microwave reactor was used for microwave reactions. Irradiation was initiated at 300 W to raise the temperature to the set point and then power was applied at intervals and levels to maintain the desired temperature. Reactions were run in sealed vessels.



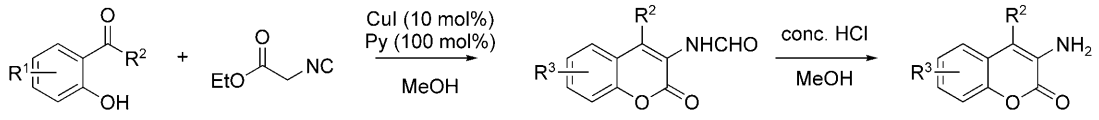
Scheme 3. Suggested reaction mechanism.

Typical Experimental Procedure for the Preparation of 2a and 3a (Table 2)

To a mixture of salicylaldehyde (**1a**, 100 mg, 0.82 mmol), ethyl isocyanoacetate (93 mg, 0.82 mmol) and pyridine (65 mg, 0.82 mmol) in MeOH (1 mL) was added CuI (16 mg, 0.08 mmol). The reaction mixture was stirred at 50 °C and monitored by TLC. After the reaction was complete (typically 4–8 h), the precipitate was isolated by filtration and washed with MeOH (2×1 mL) to give the desired product **2a** as a light yellow solid; yield: 125 mg (81%); mp 182–185 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.71$ (s, 1H), 8.58 (s, 1H), 8.31 (bs, 1H), 7.43–7.60 (m, 2H), 7.29–7.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.77$, 158.38, 150.08, 130.07, 127.88, 125.26, 124.84, 123.08, 119.48, 116.42; HR-MS (EI): $m/z = 189.0422$, calcd. for $C_{10}H_7NO_3$: 189.0426.

Compound **2a** (120 mg, 0.63 mmol) was then treated with concentated HCl (260 μL, 5 equiv.) in 10 mL of methanol, and was refluxed for 1 h. The reaction mixture was then concentrated under vacuum, and the residue was neutralized to pH ~8, and extracted with dichloromethane (50 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was removed under vacuum to afford **3a** as a yellow solid; yield: 101 mg (95%); mp 125–127 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.26$–7.34 (m, 3H), 7.15–7.25 (m, 1H), 6.71 (s, 1H), 4.27 (bs, 1H); HR-MS (EI): $m/z =$ 161.0474, calcd. for $C_9H_7NO_2$: 161.0477.

Table 2. Synthesis of 3-aminocoumarins under optimized conditions.



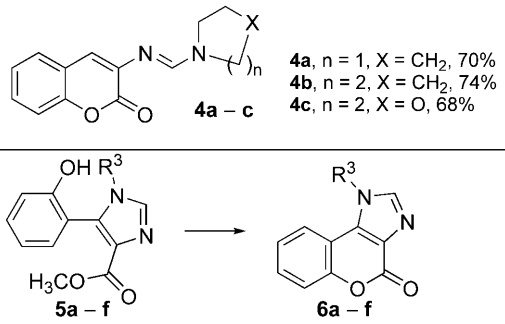
1a – j **2a – j** **3a – j**

Entry	R^1	R^2	R^3	Compound, yield (%)[a,b]	Compound, yield [%]
1	H	H	H	**2a**, 81	**3a**, 95
2	3-OMe	H	6-OMe	**2b**, 82	**3b**, 95
3	4-Et_2N	H	7-Et_2N	**2c**, 75	**3c**, 92
4	2,4-di-OMe	H	5,7-di-OMe	**2d**, 88	**3d**, 100
5	3,5-di-Cl	H	6,8-di-Cl	**2e**, 79	**3e**, 97
6	3-OMe, 5-NO_2	H	6-OMe, 8-NO_2	**2f**, 70	**3f**, 95
7	3-Br, 5-NO_2	H	6-Br, 8-NO_2	**2g**, 67	**3g**, 90
8	H	Me	H	**2h**, 63	**3h**, 93
9	4-F	Me	7-F	**2i**, 65	**3i**, 98
10	H	Et	H	**2j**, 50	**3j**, 92

[a] Yield of crystalline compound isolated by filtration (no recovery from mother liquor), hence the total yield may be higher.

[b] for entries 1–7: reaction times are 5–6 h; for entries 8 and 9: reaction time was prolonged to 24 h; for entry 10: 48 h was needed for completion of the reaction.

Table 3. Scope of the three-component reaction.



4a – c

4a, n = 1, X = CH_2, 70%
4b, n = 2, X = CH_2, 74%
4c, n = 2, X = O, 68%

5a – f **6a – f**

5a, R^3 = 4-methoxybenzyl, 70%
5b, R^3 = phenyl, 57%
5c, R^3 = 4-methoxyphenyl, 62%
5d, R^3 = *i*-propyl, 66%
5e, R^3 = cyclohexylmethyl, 63%
5f, R^3 = 4-methoxyphenethyl, 76%

6a, 88%
6b, 90%
6c, 86%
6d, 80%
6e, 85%
6f, 83%

Typical Experimental Procedure for the Preparation of 4b (Table 3)

To a mixture of salicylaldehyde (**1a**, 100 mg, 0.82 mmol), ethyl isocyanoacetate (90 μL, 0.82 mmol) and piperidine (243 μL, 2.46 mmol) in MeOH (3 mL) was added pyridine (66 μL, 0.82 mmol) and CuI (16 mg, 0.08 mmol). The reaction mixture was stirred at 50 °C overnight. The solvent was removed under vacuum, and the residue was purified by a flash column chromatography to afford **4b** as a yellow solid; yield: 155 mg (74%); mp 135–138 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.08 (s, 1H), 7.51 (dd, J = 7.7, 1.5 Hz, 1H), 7.33–7.40 (m, 1H), 7.23–7.32 (m, 2H), 7.22 (s, 1H), 3.55 (t, J = 5.3 Hz, 2H), 3.33–3.40 (m, 2H), 1.59–1.66 (m, 2H), 1.47–1.57 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.58, 154.04, 150.19, 137.13, 127.99, 126.44, 124.33, 122.80, 121.09, 115.40, 49.69, 42.30, 26.25, 24.67, 24.09; HR-MS (EI): m/z = 256.1217, calcd. for $C_{15}H_{16}N_2O_2$: 256.1212.

Typical Experimental Procedure for the Preparation of 6a (Table 3)

To a mixture of salicylaldehyde (**1a**, 100 mg, 0.82 mmol), ethyl isocyanoacetate (90 μL, 0.82 mmol) and 4-methoxybenzylamine (106 μL, 0.82 mmol) in MeOH (3 mL) was added pyridine (66 μL, 0.82 mmol) and CuI (16 mg, 0.08 mmol). The reaction mixture was stirred at 50 °C overnight. The solvent was removed under vacuum, and the residue was purified by a flash column chromatography to afford the intermediate **5a** as a pale white solid; yield: 195 mg (70%); mp 199–202 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.88 (s, 1H), 7.28 (t, J = 7.6 Hz, 1H), 6.99 (dd, J = 13.9, 7.6 Hz, 2H), 6.84 (t, J = 8.0 Hz, 3H), 6.76–6.80 (m, 2H), 4.76–5.12 (m, 2H), 3.68 (s, 3H), 3.56 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.98, 158.72, 155.03, 137.95, 135.61, 132.60, 130.56, 129.34, 128.85 (2×C), 128.65, 118.82, 115.93, 115.48, 113.88 (2×C), 55.10, 50.73, 47.76; HR-MS (EI): m/z = 338.1267, calcd. for $C_{19}H_{18}N_2O_4$: 338.1267.

A Biotage Microwave Vial (5 mL) was charged with **5a** (150 mg, 0.44 mmol) and potassium carbonate (61 mg, 0.44 mmol) in DMF (1 mL). After sealing the cap, the resulting mixture was irradiated at 180 °C for 10 min using a Biotage Initiator microwave reactor. After the reaction had cooled to ambient temperature, the crude reaction mixture was extracted with ethyl acetate (3×15 mL). The combined organic phase was washed with water (2×15 mL), brine (20 mL), dried with Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on Combiflash™ to provide the desired product as a white solid; yield: 120 mg (88%). mp 187–190 °C; ^{1}H NMR (400 MHz,

$CDCl_3$): $\delta = 7.77$ (s, 1H), 7.64 (d, $J = 8.2$ Hz, 1H), 7.42–7.50 (m, 2H), 7.22 (ddd, $J = 8.1$, 6.4, 2.1 Hz, 1H), 7.10 (d, $J = 8.8$ Hz, 2H), 6.89–6.95 (m, 2H), 5.59 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.86$, 156.86, 152.19, 143.12, 135.41, 129.70, 127.88 (2×C), 127.80, 125.53, 124.29, 121.33, 118.18, 114.86 (2×C), 112.92, 55.32, 50.62; HR-MS (EI): $m/z = 306.1005$, calcd. for $C_{18}H_{14}N_2O_3$: 306.1004.

Acknowledgements

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[12] CCDC 809175 (**2a**), CCDC 809176 (**4b**) and CCDC 809174 (**5a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[13] For an example of copper-catalyzed reactions of isocyanides, see: S. Kamijo, C. Kanazawa, Y. Yamamoto *J. Am. Chem. Soc.* **2005**, *127*, 9260–9266; and references therein.

[14] J. E. Bergmann, *Patent* WO200129049, Apr 26, **2001**.

