The Michael Reaction of *N*-Cinnamoylazoles with Phenols. A Simple Synthesis of 4-Arylchroman-2-ones and 1-Arylbenzo[*f*]chroman-3-ones

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Abstract: 4-Arylchroman-2-ones **3** and 1-arylbenzo[*f*]chroman-3-ones **6** have been prepared in moderate to good yields by reaction of dihydric or trihydric phenols with *p*-substituted *N*-cinnamoylazoles in dichloromethane under reflux in the presence of DBU.

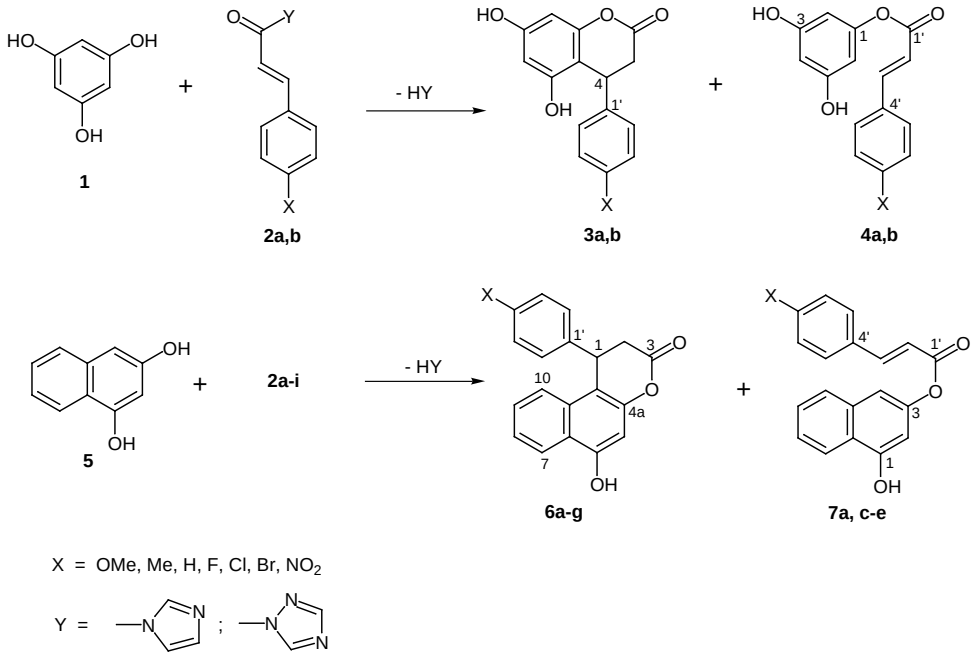
Key words: Michael reaction, *N*-cinnamoylazoles, 4-arylchroman-2-ones, 1-arylbenzo[*f*]chroman-3-ones, phenols

The hydroxy- and/or methoxy-substituted 4-arylchroman-2-one system is of relevant interest in that it is present in a number of natural molecules, e.g. neoflavonoids.[1] In addition it represents a valuable intermediate in the preparation of 4-arylcoumarins.[2]

The simplest synthetic approach to 4-arylchroman-2-ones consists in the condensation of phenols with cinnamic acids (or methyl cinnamates) as well as in the cyclization of phenyl cinnamates. Strong acidic media and different Lewis acids have been widely explored to construct the heterocyclic ring, but complex mixtures of reaction products were observed in all cases.[3]

We have recently shown that 4-arylchroman-2-ones **3** and 1-arylbenzo[*f*]chroman-3-ones **6** can be easily obtained by the one-pot two-component [3+3] coupling reaction[4] depicted in the Scheme (Y = OMe; reaction conditions : *o*-xylene under reflux without any catalyst added).[3] This reaction provides especially high yields in lactones when the cinnamate educt bears an electron-releasing group in the *para* position. Thus, in accordance with this tendency, no reaction was observed with methyl *p*-nitrocinnamate.

We report here a novel mild procedure, which can be regarded as complementary to that mentioned above. In fact, it appears to be particularly convenient for preparing compounds such as **3** and **6** wherein X is an electron-withdrawing group. This method (Scheme, Y = *N*-azolyl group) is based on the conjugated additions[5] of di- and trihydric phenols to *N-(E)*-cinnamoylazoles ("azolides")[6] in which the masked carboxy group promotes the attack of both a soft nucleophile on the β-carbon (C−C bond formation) and of a hard nucleophile on the carbonyl group (O−C bond formation).



Scheme

See Table 1 for substituents on specific compounds

Table 1 Condensation of Di- and Trihydric Phenols with *N*-Cinnamoylazoles in the Presence of DBU

Entry	Reagents	X	Y[a]	Solvent under reflux	Reaction time (h)	Product[b]/Yield (%)[c]	L/E[d]
1	**1**/**2a**	H	Im	CH_2Cl_2	2.0	**3a**/38 ; **4a**/17	2.2
2	**1**/**2b**	NO_2	Im	CH_2Cl_2	1.5	**3b**/55 ; **4b**/5	11.0
3	**5**/**2c**	OMe	Im	CH_2Cl_2	2.0	**6c**/31 ; **7c**/30	1.0
4	**5**/**2d**	Me	Im	CH_2Cl_2	2.0	**6d**/37 ; **7d**/15	2.5
5	**5**/**2a**	H	Im	CH_2Cl_2	1.5	**6a**/50 ; **7a**/12	4.1
6	**5**/**2e**	F	Im	CH_2Cl_2	2.5	**6e**/62 ; **7e**/9	6.8
7	**5**/**2f**	Cl	Im	CH_2Cl_2	1.5	**6f**/75	
8	**5**/**2g**	Br	Im	CH_2Cl_2	1.5	**6g**/72	
9	**5**/**2b**	NO_2	Im	CH_2Cl_2	1.0	**6b**/80	
10	**5**/**2h**	OMe	Taz	THF	2.0	**6c**/51 ; **7c**/21	2.4
11	**5**/**2i**	H	Taz	THF	2.0	**6a**/67 ; **7a**/13	5.2

[a] Im = *N*-imidazolyl, Taz = 1,2,4-triazol-1-yl.
[b] All compounds gave satisfactory elemental analyses: C ± 0.35, H ± 0.29.
[c] Isolated yields from cinnamic acids.
[d] Lactone/ester ratio.

The general procedure described below was used for preparing the 4-arylchroman-2-ones **3a**,**b** and the 1-arylbenzo[*f*]chroman-3-ones **6a−g** listed in Table 1. The structure of each product was confirmed by the spectral data reported in Table 2.

The solvent of general applicability for the condensation of imidazolides with phenols appears to be dichloromethane under reflux. Other polar solvents, e.g. hydrogen-bond acceptors such as THF and DMSO, afforded, even at different temperatures, lower yields in lactones (and higher in esters). An approximate. 1:1 molar ratio between the phenolic educt and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was found to be optimal. We have also examined a few other azolides as conjugate acceptors using naphthoresorcinol (**5**) as reference donor and varying the azolyl group [4(5)-nitroimidazol-1-yl,[7] 1,2,4-triazol-1-yl,[8] 1,2,3-triazol-1(2)-yl[9]], the *para*-substituent on the benzene ring, and the solvent. Satisfactory yields in chromanones were obtained with only two 1,2,4-triazolides (entries 10 and 11, Table 1), the solvent being THF in both cases.

As concerns the reactivity of phenolic educts, it must be noted that monohydric phenols and naphthols (as well as resorcinol) did not give rise to the corresponding chromanones even when the counterpart was the highly reactive *N*-(*p*-nitrocinnamoyl)imidazole.

From a mechanistic point of view, it is reasonable to assume an initial conjugate addition[5] followed by lactone formation.[6] An alternative path, wherein these two bond-forming steps are reversed, is to be ruled out by the observation that aryl cinnamates **4** and **7** are not converted into the corresponding chromanones **3** and **6**, respectively, under the reaction conditions.

It can be noticed that the yields in chromanones from experiments 3−6 (Table 1), and also the corresponding ratios between the 1,4- and 1,2-adducts (L/E), roughly correlate with the Hammet constants[10] of the substituents on the *N*-cinnamoylimidazole.

Azolides, usually imidazolides, are well recognised reactive forms of carboxylic acids for preparing esters, amides and other derivatives.[6] However, to our knowledge, the 1,4-addition of phenols to *N*-cinnamoylazoles is an unprecedented example of the use of α,β-unsaturated azolides as conjugate acceptors in a base-promoted Michael reaction.[5]

Mps (Büchi apparatus) are uncorrected. Microanalyses were obtained with a Perkin-Elmer 240 Elemental Analyzer. ^{1}H- and ^{13}C NMR spectra were recorded on a Bruker AC 300 or on a Bruker AC 200 spectrometer in DMSO-d_6, using the solvent signal as internal standard (δ_H 2.50, δ_C 39.50). Silica gel (Merck, 40−63 μm) was used for flash chromatography. Analytical TLC was performed on Si gel 60 F_{254} aluminum sheets (0.2 mm thickness, Merck) using the following eluents: A ($CHCl_3$:EtOAc, 3:5), B ($CHCl_3$:EtOAc, 5:1).

All reagents were of commercial quality or purified prior to use by standard methods. Cinnamic acid, *p*-methoxy-, and *p*-nitrocinnamic acids were commercially available. The other cinnamic acids were synthesized by condensation of the corresponding aldehydes with malonic acid in pyridine soln in the presence of piperidine.[11]

Compounds 3 and 6; General Procedure

To a soln of cinnamoyl chloride (prepared from 1.2 mmol of cinnamic acid by the standard procedure using oxalyl chloride) in an-

Table 2 Chromanones (**3a,b**, **6a–g**) Prepared

Product	R_f (eluent)[a]	Mp (°C)	^{1}H NMR (DMSO-d_6) δ, *J* (Hz)	^{13}C NMR (DMSO-d_6) δ
3a	0.52 (A)	209–210 (Lit[16] 210–211)	2.86 (br d, 1 H, *J* = 15.6, H-3a), 3.21 (dd, 1 H, *J* = 15.6, 6.8, H-3b), 4.49 (br d, 1 H, *J* = 6.8, H-4), 6.07 (d, 1 H, *J* = 2.1) and 6.22 (d, 1 H, *J* = 2.1) (H-6, H-8), 7.09–7.13 (m, 2 H) and 7.21–7.30 (m, 3 H) (Ar-H), 9.48 (s, 1 H) and 9.65 (s, 1 H) (5-OH, 7-OH)	33.88, 37.11, 94.88, 98.98, 103.81, 126.66, 128.58, 142.56, 153.06, 155.43, 158.02, 167.73
3b	0.49 (A)	210–212	2.87 (br d, 1 H, *J* = 15.7, H-3a), 3.28 (dd, 1 H, *J* = 15.7, 6.5, H-3b), 4.56 (br d, 1 H, *J* = 6.5, H-4), 6.03 (br s, 1 H) and 6.17 (br s, 1 H) (H-6, H-8), 7.34 (d, 2 H, *J* = 8.5, H-2', H-6'), 8.14 (d, 2 H, *J* = 8.5, H-3', H-5'), 9.56 (s, 1 H) and 9.78 (s, 1 H) (5-OH, 7-OH)	33.90, 36.49. 94.99, 98.92, 101.92, 123.98, 128.14, 146.55, 150.43, 153.08, 155.57, 158.46, 167.41
6a	0.59 (B)	222–223	2.92 (dd, 1 H, *J* = 15.9, 1.0, H-2a), 3.45 (dd, 1 H, *J* = 15.9, 7.2, H-2b), 4.99 (dd, 1 H, *J* = 7.2, 1.0, H-1), 6.72 (s, 1H, H-5), 7.01–7.31 (m, 5 H) and 7.34–7.52 (m, 2 H) (Ar-H), 7.75 (d, 1 H, *J* = 8.2, H-10), 8.16 (d, 1 H, *J* = 8.5, H-7), 10.68 (s, 1 H, 6-OH)	36.00, 37.54, 99.10, 108.35, 122.67, 123.11, 123.82, 126.77, 127.00, 127.68, 128.88, 131.44, 142.19, 149.76, 154.40, 167.42
6b	0.56 (B)	182–184	2.99 (br d, 1 H, *J* = 16.0, H-2a), 3.55 (dd, 1 H, *J* = 16.0, 7.1, H-2b), 5.21 (br d, 1 H, *J* = 7.1, H-1), 6.75 (s, 1 H, H-5), 7.41 (d, 2 H, *J* = 8.6, H-2', H-6'), 7.38–7.53 (m, 2 H, H-8, H-9), 7.74 (d, 1 H, *J* = 8.1, H-10), 8.15 (d, 2 H, *J* = 8.6, H-3', H-5'), 8.18 (d, 1 H, *J* = 8.3, H-7), 10.76 (s, 1 H, 6-OH)	35.78, 36.99, 99.20, 107.27, 122.89, 123.00, 124.11, 124.21, 128.02, 128.42, 128.72, 131.37, 131.65, 146.74, 149.98, 154.88, 167.07
6c	0.55 (B)	176–178 (Lit[15] 176–178)	see Ref. 15	see Ref. 15
6d	0.62 (B)	174–177	2.22 (s, 3 H, CH_3), 2.90 (br d, 1 H, *J* = 16.5, H-2a), 3.42 (dd, 1H, *J* = 16.5, 6.9, H-2b), 4.95 (br d, 1H, *J* = 6.9, H-1), 6.74 (s, 1 H, H-5), 7.01 (d, 2 H, *J* = 8.6) and 7.10 (d, 2 H, *J* = 8.6) (H-2', H-3', H-5', H-6'), 7.35–7.57 (m, 2 H, H-8, H-9), 7.75 (d, 1 H, *J* = 8.4, H-10), 8.14 (d, 1 H, *J* = 8.4, H-7), 10.67 (s, 1 H, 6-OH)	20.38, 35.57, 37.53, 99.00, 108.42, 122.55, 123.02, 123.66, 126.54, 127.50, 128.64, 129.32, 131.34, 136.07, 139.04, 149.59, 154.22, 167.34
6e	0.61 (B)	215–217	2.96 (br d, 1 H, *J* = 15.8, H-2a), 3.45 (dd, 1 H, *J* = 15.8, 7.0, H-2b), 5.04 (br d, 1 H, *J* = 7.0, H-1), 6.75 (s, 1 H, H-5), 7.08–7.24 (m, 4 H, H-2', H-3', H-5', H-6'), 7.42 (approx. t, 1 H, *J* = 7.5) and 7.51 (app t, 1 H, *J* = 7.5) (H-8, H-9), 7.76 (d, 1 H, *J* = 8.3, H-10), 8.19 (d, 1 H, *J* = 8.2, H-7), 10.66 (s, 1 H, 6-OH)	35.12, 37.44, 99.03, 107.97, 115.51 ($^2J_{C,F}$ = 21 Hz), 122.61, 122.91, 12§.74, 127.63, 128.63 ($^3J_{C,F}$ = 5 Hz), 131.21, 137.78, 149.38, 154.46, 160.86 ($^1J_{C,F}$ = 246 Hz), 167.00
6f	0.57 (B)	210–211	2.93 (br d, 1 H, *J* = 15.6, H-2a), 3.47 (dd, 1 H, *J* = 15.6, 7.0, H-2b), 5.02 (br d, 1 H, *J* = 7.0, H-1), 6.71 (s, 1 H, H-5), 7.13 (d, 2 H, *J* = 8.7, H-2', H-6'), 7.32 (d, 2 H, *J* = 8.7, H-3', H-5'), 7.35–7.58 (m, 2 H, H-8, H-9), 7.75 (d, 1 H, *J* = 8.1, H-10), 8.17 (d, 1 H, *J* = 8.2, H-7), 10.66 (s, 1 H, 6-OH)	35.23, 37.22, 99.02, 107.80, 122.62, 122.89, 123.78, 127.66, 128.64, 128.74, 131.24, 131.63, 141.00, 149.72, 154.47, 167.11
6g	0.57 (B)	230–232	2.93 (br d, 1 H, *J* = 15.2, H-2a), 3.46 (dd, 1 H, *J* = 15.2, 7.2, H-2b), 5.02 (br d, 1 H, *J* = 7.2, H-1), 6.64 (s, 1 H, H-5), 7.08 (d, 2 H, *J* = 7.9, H-2', H-6'), 7.49 (d, 2 H, *J* = 7.9, H-3', H-5'), 7.35–7.58 (m, 2 H, H-8, H-9), 7.73 (d, 1 H, *J* = 8.0, H-10), 8.18 (d, 1 H, *J* = 8.0, H-7), 10.65 (s, 1 H, 6-OH)	35.28, 37.14, 99.00, 107.73, 120.08, 122.60, 122.90, 123.78, 127.67, 129.00, 131.24, 131.68, 141.46, 149.71, 154.45, 167.10

[a] See experimental section for eluents.

hyd CH_2Cl_2 (5 mL) was added dropwise a soln of imidazole (2.4 mmol) in anhyd CH_2Cl_2 (10 mL) at 0 °C. After stirring for 1 h at r.t., the precipitated imidazolium chloride was filtered off and the filtrate was evaporated under reduced pressure. The resulting *N*-cinnamoylimidazole (87% yield), mp 131−133 °C (Lit.[12] mp 133−134 °C), was used in the next step without further purification. The other *N*-acylazoles were prepared in a similar manner[6] in ≥ 80% yield using dry CH_2Cl_2 or THF as solvent.

To a suspension of the phenol and of the *N*-acylazole, as obtained above, (1:1 molar ratio) in dry CH_2Cl_2 (or THF) (10 mL) under N_2 was added DBU (1.5 mL) in anhyd CH_2Cl_2 (or THF) (5 mL). The reaction mixture was refluxed with stirring until TLC (eluent A or B) showed complete disappearance of the phenol, and then acidified with 0.2 N HCl. The organic layer was separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4), filtered, concentrated under reduced pressure and the residue chromatographed on silica gel using a $CHCl_3$/

EtOAc gradient for elution. Each isolated product was recrystallized from proper solvent and its purity checked by TLC and elemental analysis.

4a: R_f = 0.62 (eluent A); mp 198−200 °C (Lit.[13] mp 200−202 °C), see reference 14 for NMR data.

4b: R_f = 0.54 (eluent A); mp 231−233 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.09 (br s, 2H) and 6.18 (d, 1H, J = 2.0 Hz) (H-2, H-4, H-6), 7.02 (d, 1H, J = 16.0 Hz, H-2′), 7.94 (d, 1H, J = 16.0 Hz, H-3′), 8.10 (d, 2H, J = 8.5 Hz, H-5′, H-9′), 8.29 (d, 2H, J = 8.5 Hz, H-6′, H-8′), 9.52 (s, 2H, 3-OH, 5-OH).

7a: R_f = 0.68 (eluent B); mp 144−146 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 6.71 (d, 1H, J = 2.0 Hz) and 7.19 (d, 1H, J = 2.0 Hz) (H-2, H-4), 6.92 (d, 1H, J = 16.0 Hz, H-2′), 7.40−7.56 (m, 5H) and 7.69−7.85 (m, 3H) (Ar-H), 7.90 (d, 1H, J = 16.0 Hz, H-3′), 8.13 (d, 1H, J = 8.2 Hz, Ar-H), 10.52 (s, 1H, 1-OH).

7c: R_f = 0.66 (eluent B); mp 167−169 °C, see reference 15 for NMR data.

7d: R_f = 0.67 (eluent B); mp 131−134 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.33 (s, 3H, CH_3), 6.72 (brs, 1H, Ar-H), 6.87 (d, 1H, J = 16.0 Hz, H-2′), 7.03−7.86 (m, 9H, Ar-H and H-3′), 8.13 (d, 1H, J = 8.0 Hz, Ar-H), 10.51 (s, 1H, 1-OH).

7e: R_f = 0.68 (eluent B); mp 135−137 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 7.00−7.17 (m, 3H), 7.31−7.49 (m, 4H), 7.73−7.80 (m, 2H), 7.94−8.03 (m, 3H), 9.56 (s, 1H, 1-OH).

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