An Efficient Synthesis of 3-(1*H*-Tetrazol-5-yl)coumarins (= 3-(1*H*-Tetrazol-5-yl)-2*H*-1-benzopyran-2-ones) *via* Domino *Knoevenagel* Condensation, *Pinner* Reaction, and 1,3-Dipolar Cycloaddition in Water

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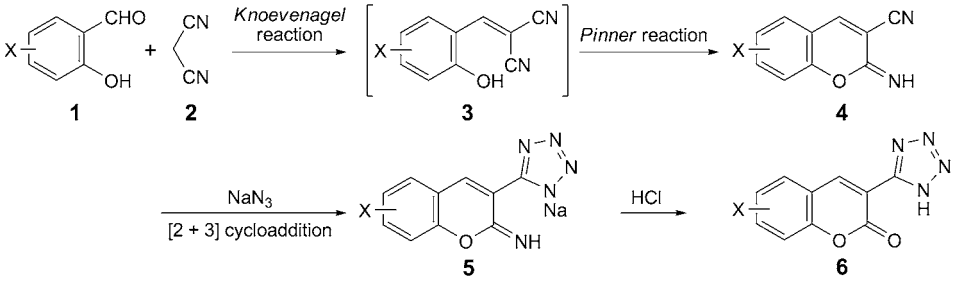
A novel straightforward synthesis of 3-(1*H*-tetrazol-5-yl)coumarins (= 3-(1*H*-tetrazol-5-yl)-2*H*-1-benzopyran-2-ones) **6** *via* domino *Knoevenagel* condensation, *Pinner* reaction, and 1,3-dipolar cycloaddition of substituted salicylaldehydes (=2-hydroxybenzaldehydes), malononitrile (propanedinitrile), and sodium azide in H_2O is reported (*Scheme 1* and *Table 2*). This general protocol provides a wide variety of 3-(1*H*-tetrazol-5-yl)coumarins in good yields under mild reaction conditions.

Introduction. – The 1*H*- and 2*H*-tetrazoles are regarded as isosteric replacements of carboxylic acids with improved properties in drug metabolism and pharmacokinetics. Thus, they are frequently employed in the lead optimization of ethical-drug candidates to enhance the oral bioavailability. Several successful examples of this way of proceeding are present in the sartane drug family, which is used to treat hypertension [1–3]. Also this heterocycle plays a role in coordination chemistry as a ligand, and in various materials-science applications including propellants [4] and explosives [5]. Furthermore, tetrazole moieties are important synthons in synthetic organic chemistry [6]. Therefore, a number of methods have been reported for the preparation of tetrazoles [7–13]. The [2 + 3] cycloaddition of nitriles and azides is a reliable synthetic route to tetrazole formation [14–18]. However, many of these protocols have some disadvantages such as the use of toxic metals, strong *Lewis* acid, or expensive reagents, low yield, harsh reaction conditions, H_2O sensitivity, and the presence of hydrazoic acid, which is toxic and explosive. Recently, coumarins and tetrazoles have attracted great attention, however, compounds incorporating both coumarin and tetrazole motifs have seldom been described [19–23].

Herein, we report an efficient, facile, and eco-friendly process for the synthesis of 3-(1*H*-tetrazol-5-yl)coumarins (= 3-(1*H*-tetrazol-5-yl)-2*H*-1-benzopyran-2-ones) *via* one-pot domino chemistry.

Results and Discussion. – The proposed way of proceeding for the synthesis of 3-(1*H*-tetrazol-5-yl)coumarins **6** is depicted in *Scheme 1*. The 3-(1*H*-tetrazol-5-yl)-coumarins **6** were produced by acid hydrolysis of **5**. The intermediate **5** was assembled from the [2 + 3] cycloaddition reaction of 2*H*-1-benzopyran-3-carbonitriles **4** and NaN_3, and the carbonitriles **4** were synthetically accessible by a *Knoevenagel* (**1** + **2** → **3**) followed by a *Pinner* reaction (**3** → **4**).

Scheme 1



This one-pot reaction was investigated in different solvents without any catalyst (*Table 1*) with a simple model substrate. Salicylaldehyde (=2-hydroxybenzaldehyde; **1a**; 1 mmol) and malononitrile (= propanedinitrile; **2**; 1 mmol) were stirred at room temperature in various solvents for 3 h, then NaN_3 (1.5 mmol) was added, and the mixture was heated under reflux for 10 h (*Table 1*), followed by hydrolysis with 3N HCl at room temperature for 30 min. As can be seen from *Table 1*, **6a** was scarcely obtained in nonpolar solvents (*Entries 1* and *2*), and even EtOH as a polar protic solvent failed to produce **6a** in good yield (*Entry 3*). The addition of H_2O to the EtOH solution improved the yield of **6a** (*Entries 4* and *5*), and interestingly, when the reaction was performed in H_2O, **6a** was obtained in high yield (*Entry 6*).

Table 1. *Model Reaction with Salicylaldehyde* (**1a**; X = H)*, Malononitrile* (**2**)*, and* NaN_3[a])

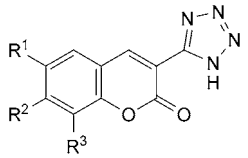
Entry	Solvent	Yield of **6a** [%]
1	toluene	trace
2	$CHCl_3$	trace
3	EtOH	51
4	H_2O/EtOH 1:1	64
5	H_2O/EtOH 7:3	75
6	H_2O	91

[a]) Reaction time: 3 h at r.t., followed by addition of NaN_3 and heating to reflux for 10 h.

To explore the scope and limitations of the reaction, the procedure was extended to various salicylaldehydes **1b**–**1g**. As indicated in *Table 2*, the reactions proceeded very efficiently and led to the formation of the corresponding 3-(1*H*-tetrazol-5-yl)coumarins **6b**–**6g** in high yields. The reaction took place very cleanly under mild conditions in the absence of any catalyst. These catalyst-free reactions carried out in H_2O are considerably safer, nontoxic, environmentally friendly, and inexpensive.

To further explore the potential of this one-pot domino protocol for the synthesis of tetrazolylcoumarins **6**, we replaced salicylaldehyde (**1a**) by 3-hydroxynaphthalene-2-carboxaldehyde (**7**) and obtained 3-(1*H*-tetrazol-5-yl)-2*H*-naphtho[2,3-*b*]pyran-2-one (**8**) in 85% yield under the same reaction conditions (*Scheme 2*).

Table 2. *Synthesis of 3-(1*H*-Tetrazol-5-yl)coumarins* **6a**–**6g**

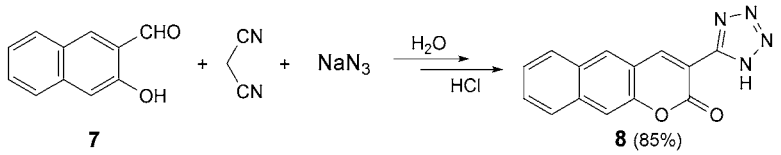


6a – 6g

Product	R^1	R^2	R^3	Yield [%][a])
6a	H	H	H	91
6b	H	H	MeO	88
6c	H	MeO	H	89
6d	MeO	H	H	90
6e	OH	H	H	86
6f	H	Br	H	85
6g	Br	H	H	91

[a]) Isolated yield.

Scheme 2



The structures of the isolated products **6a**–**6f** and **8** were deduced from their elemental analyses, IR, and ^{1}H- and ^{13}C-NMR spectra. The MS of these compounds displayed molecular-ion peaks at the appropriate *m*/*z* values. Thus, the MS of **6a** showed the molecular-ion peak at *m*/*z* 214; its IR spectrum (KBr) absorption bands for the NH and C=O groups at 3393 and 1713 cm^{-1}, respectively, and its ^{1}H-NMR spectrum two *s* (δ(H) 8.97 and 16.38) for H–C(4) and H–N(1′) along with a *m* (δ(H) 7.43–8.25) for H–C(5), H–C(6), H–C(7), and H–C(8). The ^{1}H-decoupled ^{13}C-NMR spectra of **6a** exhibited 10 distinct resonances that confirmed the proposed structure.

In conclusion, an efficient, plain, and convenient method for the preparation of new 3-(1*H*-tetrazol-5-yl)coumarins in H_2O is reported.

Experimental Part

General. The chemicals used were obtained from *Fluka* and *Merck* and were applied without purification. M.p.: *Electrothermal-9100* apparatus; uncorrected. IR Spectra (KBr): *Bomem-MB*-FT-IR apparatus; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker-DRX-300-Avance* spectrometer; at 300.13 (^{1}H) and 75.47 MHz (^{13}C) in (D_6)DMSO; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. EI-MS (70 eV): *Finnigan-MAT-8430* mass spectrometer; in *m*/*z*. Elemental analyses: *Heraeus-CHN-O-Rapid* analyzer.

*3-(1*H*-Tetrazol-5-yl)-2*H*-1-benzopyran-2-one* (**6a**): *Typical Procedure.* A mixture of salicylaldehyde (**1a**; 1 mmol) and malononitrile (**2**; 1 mmol) in H_2O (5 ml) was stirred at r.t. for 3 h. To this mixture was added NaN_3 (1.5 mmol), followed by heating under reflux for 10 h. The mixture was filtered, and to the

filtrate was added 3N HCl (20 ml) with vigorous stirring causing the precipitation of **6a**. The precipitate was filtered and dried in a drying oven: **6a** (019 g, 91%). Off-white powder. M.p. 228–230°. IR: 3393, 1713, 1606, 1555, 1461. ^{1}H-NMR: 7.43–7.51 (*m*, 1 arom. H); 7.8–8.04 (*m*, 2 arom. H); 8.21–8.25 (*m*, 1 arom. H); 8.97 (*s*, H–C(4)); 16.38 (*s*, NH). ^{13}C-NMR: 97.9; 101.4; 111.7; 114.3; 155.5; 131.7; 153.8; 157.0; 157.8; 165.8. EI-MS: 214 (M^+). Anal. calc. for $C_{10}H_6N_4O_2$: C 56.08, H 2.82, N 26.16; found: C 55.95, H 2.90, N 26.07.

*8-Methoxy-3-(1*H*-tetrazol-5-yl)-2*H*-1-benzopyran-2-one* (**6b**): Off-white powder (0.21 g, 88%). M.p. 240–242°. IR: 3444, 1738, 1606, 1555, 1480. ^{1}H-NMR: 3.90 (*s*, MeO); 7.03–7.11 (*m*, 2 arom. H); 7.71 (*d*, $^3J = 8.7$, 1 arom. H); 8.83 (*s*, H–C(4)); 16.41 (*s*, NH). ^{13}C-NMR: 56.6; 112.9; 116.3; 119.3; 121.3; 125.6; 143.3; 144.9; 146.8; 149.9; 158.2. EI-MS: 244 (M^+). Anal. calc. for $C_{11}H_8N_4O_3$: C 54.10, H 3.30, N 22.94; found: C 54.22, H 3.25, N 22.83.

*7-Methoxy-3-(1*H*-tetrazol-5-yl)-2*H*-1-benzopyran-2-one* (**6c**): Yellow powder (0.22 g, 89%). M.p. 265–267°. IR: 3330, 1713, 1606, 1568, 1524, 1498. ^{1}H-NMR: 3.88 (*s*, MeO); 7.03 (*d*, $^3J = 8.6$, 1 arom. H); 7.11 (*s*, 1 arom. H); 7.89 (*d*, $^3J = 8.6$, 1 arom. H); 8.95 (*s*, H–C(4)); 16.37 (*s*, NH). ^{13}C-NMR: 56.6; 101.0; 108.6; 112.4; 113.9; 131.6; 144.9; 150.1; 156.2; 158.8; 164.6. EI-MS: 244 (M^+). Anal. calc. for $C_{11}H_8N_4O_3$: C 54.10, H 3.30, N 22.94; found: C 54.19, H 3.23, N 22.85.

*6-Methoxy-3-(1*H*-tetrazol-5-yl)-2*H*-1-benzopyran-2-one* (**6d**): Off-white powder (0.22 g, 90%). M.p. 279–281°. IR: 3292, 1707, 1581, 1498, 1452. ^{1}H-NMR: 3.80 (*s*, MeO); 7.32 (*s*, 1 arom. H); 7.44 (*d*, $^3J = 8.0$, 1 arom. H); 7.54 (*s*, 1 arom. H); 8.95 (*s*, H–C(4)); 16.53 (*s*, NH). ^{13}C-NMR: 56.2; 112.1; 112.9; 117.9; 119.2; 122.0; 144.5; 148.5; 156.4; 158.6. EI-MS: 244 (M^+). Anal. calc. for $C_{11}H_8N_4O_3$: C 54.10, H 3.30, N 22.94; found: C 54.21, H 3.25, N 22.82.

*6-Hydroxy-3-(1*H*-tetrazol-5-yl)-2*H*-1-benzopyran-2-one* (**6e**): Off-white powder (0.20 g, 86%). M.p. 268–270°. IR: 3473, 3438, 1718, 1605, 1568, 1477. ^{1}H-NMR: 7.53 (*s*, 1 arom. H); 7.89 (*s*, 1 arom. H); 8.31 (*s*, 1 arom. H); 8.95 (*s*, H–C(4)); 16.60 (br. *s*, NH overlap with OH). ^{13}C-NMR: 113.6; 114.1; 117.3; 119.4; 120.1; 133.2; 136.3; 144.2; 153.0; 158.1. EI-MS: 230 (M^+). Anal. calc. for $C_{10}H_6N_4O_3$: C 52.18, H 2.63, N 24.34; found: C 52.25, H 2.75, N 24.42.

*7-Bromo-3-(1*H*-tetrazol-5-yl)-2*H*-1-benzopyran-2-one* (**6f**): Off-white powder (0.24 g, 85%). M.p. 270–272°. IR: 3470, 1718, 1615, 1553, 1465. ^{1}H-NMR: 7.41 (*s*, 1 arom. H); 7.68 (*s*, 1 arom. H); 8.31 (*s*, 1 arom. H); 9.05 (*s*, H–C(4)); 16.51 (*s*, NH). ^{13}C-NMR: 113.6; 115.0; 116.1; 119.3; 121.6; 133.4; 135.6; 142.3; 154.0; 159.1. EI-MS: 293 (M^+), 291 (M^+). Anal. calc. for $C_{10}H_5BrN_4O_2$: C 40.98, H 1.72, N 19.12; found: C 40.89, H 1.80, N 19.18.

*6-Bromo-3-(1*H*-tetrazol-5-yl)-2*H*-1-benzopyran-2-one* (**6g**): Off-white powder (0.26 g, 91%). M.p. 258–260°. IR: 3463, 1720, 1600, 1562, 1473. ^{1}H-NMR: 7.50 (*s*, 1 arom. H); 7.88 (*s*, 1 arom. H); 8.25 (*s*, 1 arom. H); 8.99 (*s*, H–C(4)); 16.60 (*s*, NH). ^{13}C-NMR: 113.9; 114.0; 117.1; 119.0; 120.7; 132.2; 136.4; 143.2; 153.0; 158.0. EI-MS: 293 (M^+), 291 (M^+). Anal. calc. for $C_{10}H_5BrN_4O_2$: C 40.98, H 1.72, N 19.12; found: C 40.89, H 1.80, N 19.18.

*3-(1*H*-Tetrazol-5-yl)-2*H*-naphtho[2,3-*b*]pyran-2-one* (**8**): Off-white powder (0.22 g, 85%). M.p. 231–233°. IR: 3437, 1707, 1555, 1498. ^{1}H-NMR: 7.39 (*d*, $^3J = 8.6$, 1 arom. H); 7.51 (*d*, $^3J = 8.6$, 1 arom. H); 7.87 (*t*, $^3J = 9$, 1 arom. H); 8.15 (*s*, 1 arom. H); 8.26 (*s*, 1 arom. H); 8.67 (*s*, 1 arom. H); 8.99 (*s*, H–C(4)); 16.55 (s, NH). ^{13}C-NMR: 111.5; 113, 116.9; 122.7; 122.8; 126.9; 129.2; 129.4; 130.3; 135.9; 140.3; 154.4; 158.2. EI-MS: 264 (M^+). Anal. calc. for $C_{14}H_8N_4O_2$: C 63.64, H 3.05, N 21.20; found: C 63.52, H 3.13, N 21.13.

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