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Rearrangements of *N*-alkyl-/aryl-nitrones derived from 4-oxo-4*H*-1-benzopyran-3-carboxaldehyde—a solvent-dependent process

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Abstract—*C*-(4-Oxo-4*H*-1-benzopyran-3-yl)-*N*-alkyl-/aryl-nitrones derived from 4-oxo-4*H*-1-benzopyran-3-carboxaldehyde, rearrange to 2-alkyl-/aryl-amino-3-formylchromone and/or 3-(alkyl-/aryl-aminomethylene)chroman-2,4-dione depending upon the reaction medium. 3-(Alkylaminomethylene)chroman-2,4-dione has been utilized in the synthesis of 1-benzopyrano[3,4-*d*]isoxazole-4-one.

The synthesis of heterocycles fused with a chromone moiety has attracted much attention because of their pharmacological importance.[1] 2-Alkyl-/aryl-amino-3-formylchromone **4** has been utilized recently in the synthesis of several heterocycles.[2] 3-(Arylaminomethylene)chroman-2,4-dione **5** (R′ = aryl) has been transformed into tricoumarols and coumarinoquinolines.[3] Considering 3-(alkyl-/aryl-aminomethylene)chroman-2,4-dione **5** to be a very good precursor of heterocycles fused at the 3,4-position of 1-benzopyran, we became interested in synthesizing 3-(alkylaminomethylene)chroman-2,4-diones **5** (R′ = alkyl), which are expected to be more reactive than **5** (R′ = aryl). β-Alkylamino-α,β-unsaturated ketones have been utilized in the synthesis of different heterocycles.[4] Our earlier method[3] for the synthesis of **5** (R′ = aryl) using K-10 montmorillonite and aromatic amines with **1** is difficult to accomplish with aliphatic amines. A report[5] on the thermal rearrangement of nitrone **3e** to **4e** (70%) and **5e** (25%) gave us an impetus to utilize this rearrangement as a route to our target system **5** (R′ = alkyl).

Very recently, we reported a one-pot synthesis of **4** (R′ = alkyl or aryl) from **1**[2c] and some differences in the reactivity of *N*-alkyl- and *N*-aryl nitrones **3** towards hydrolysis reactions.[6] In continuation of our studies on the reactivities of nitrones **3**, we report herein the solvent-directed rearrangement of nitrones **3** to **4** and/or **5** and conversion of **5** (R′ = alkyl) to coumarino[3,4-*d*]-isoxazole.

Nitrones **3** (R′ = alkyl) were prepared by reaction of **1** with nitroalkanes **2** and Zn in the presence of HOAc in EtOH under an inert atmosphere.[6] Nitrones **3** were heated under reflux in different solvents for varying times to obtain **4** and/or **5** (Table 1).

It was observed that polar solvents facilitated the formation of **4**, whereas nonpolar solvents allow the formation of both **4** and **5**. The rearrangement of **3b** to **4b** takes place in 7 h when heated under reflux in methanol but needs only 2 h in ethanol (entries 1, 2 and 3), which indicates that higher temperatures facilitate this rearrangement. However, the same transformation is incomplete even after heating under reflux for 41 h in benzene (entry 4). Thus, the polarity of the solvent also has some effect on the rearrangement. To check the necessity for a protic solvent, the same transformation was also carried out in dipolar aprotic solvents. The rearrangement was complete in 2 h when heated at reflux in acetonitrile (entry 5) and for 30 h in acetone (entry 6). Comparing the rearrangements in MeOH [bp 65 °C, dielectric constant (∈) 32.7], EtOH (bp 78 °C, ∈24.6), benzene (bp 80 °C, ∈2.3), CH_3CN (bp 82 °C, ∈37.5) and acetone (bp 56 °C, ∈20.7), it is clear that a protic solvent has little effect on this rearrangement but the outcome of the rearrangement depends on the polarity of the solvent and also on the temperature. On heating in benzene

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Table 1. Compounds **4** and **5** prepared from nitrones **3** by heating in different solvents

Entry	Nitrone	R	R′	Medium	Time/h	% Yield of **4**[a]	Mp of **5** (°C) (*E*+*Z*)	% Yield of **5**	*E*:*Z* of **5**
1	**3a**	H	Et	MeOH	7	98	—	—	—
2	**3b**	Me	Et	MeOH	7	95	—	—	—
3	**3b**	Me	Et	EtOH	2	98	—	—	—
4	**3b**	Me	Et	C_6H_6	41[b]	30	188–90	40	2:5
5	**3b**	Me	Et	CH_3CN	2	90	—	—	—
6	**3b**	Me	Et	Acetone	30	80	—	—	—
7	**3a**	H	Et	MeOH/ TsOH	5	95	—	—	—
8	**3b**	Me	Et	Toluene	14	20	186–88	60	1:3
9	**3b**	Me	Et	Xylene	2	10	188–90	70	2:5
10	**3b**	Me	Et	Benzene/ TsOH	1	90	—	—	—
11	**3b**	Me	Et	AcOH[c]	4.5	90	—	—	—
12	**3a**	H	Et	Xylene	2	10	184–86	70	2:5
13	**3c**	H	Me	Xylene	2	20	194–96	65	1:2
14	**3d**	Me	Me	Xylene	2	15	192–94	72	1:2
15	**3f**	H	Ar[d]	Toluene	6	15	194–97	70	5:2
16	**3g**	Me	Ar[d]	Toluene	7	17	186–90	70	1:2
17	**3g**	Me	Ar[d]	Xylene	2	10	188–90	85	1:2
18	**3e**	H	Ph	MeOH	14		No reaction		
19	**3f**	H	Ar[d]	MeOH	20		No reaction		
20	**3g**	Me	Ar[d]	MeOH	20		No reaction		
21	**3g**	Me	Ar[d]	EtOH	4	90	—	—	—
22	**3g**	Me	Ar[d]	Benzene/ TsOH	4	60	—	—	—
23	**3g**	Me	Ar[d]	CH_3CN	2	90	—	—	—
24	**3g**	Me	Ar[d]	AcOH[c]	10	95	—	—	—

[a] All compounds have the same mp and mmp with authentic samples.[2c]
[b] 10% Unreacted starting material was recovered.
[c] Reactions were carried out at room temperature with stirring.
[d] Ar stands for C_6H_4Me-*p*.

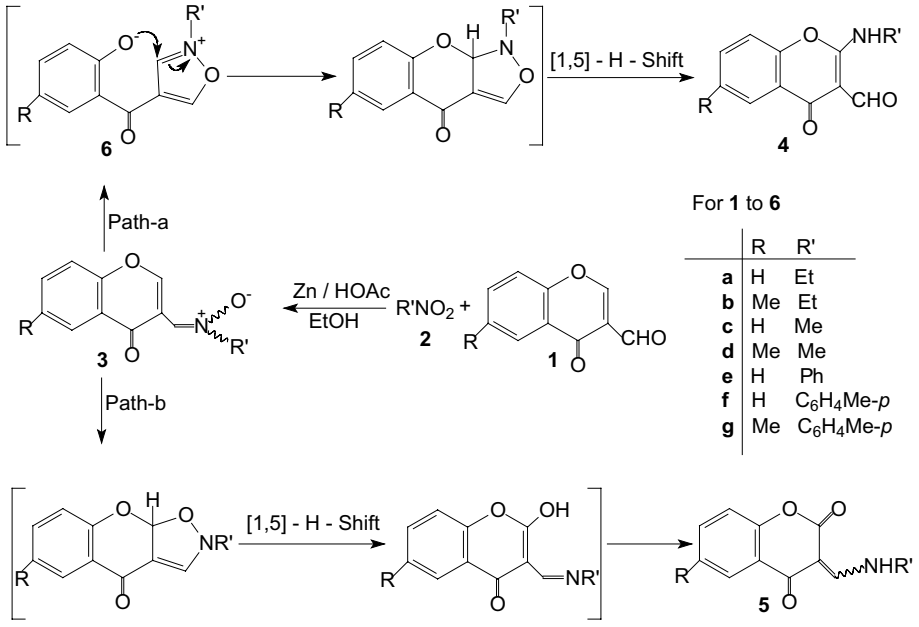
(entry 4), **3b** gave a mixture of **4b** and **5b**. Like compound **5** (R′ = aryl),[3,5] compound **5** (R′ = alkyl) showed a single spot on TLC, however, ^1H NMR measurements showed a diastereomeric mixture (*E* and *Z*).[7] The higher deshielding effect on the β-H when *cis* to the ester function in an α,β-unsaturated ester compared to an α,β-unsaturated ketone[8] helped to distinguish the *E* and *Z* isomers. From these observations it is presumed that, although the transformation of **3** to **4** is guided both by the polarity of the solvent and heating, the transformation of **3** to **5** is only thermally controlled. Based on this, the above rearrangement was carried out in toluene and xylene (entries 8 and 9), where the reaction times were 14 h and 2 h, respectively. The yield of **5** was also found to increase on changing the solvent from toluene to xylene. Interestingly, the rearrangement of **3b** in benzene was complete in 1 h on adding a trace of *p*-toluenesulfonic acid and compound **4b** was the only product (entry 10). The addition of TsOH to a methanolic solution of **3a** also enhanced the reaction rate (entry 7). The rearrangement of **3b** to **4b** can also be accomplished by stirring **3b** in AcOH at room temperature (entry 11).

The *N*-aryl nitrones **3e**–**g** were also heated under reflux in various solvents (entries 15–23). The results are similar to those using the *N*-alkyl nitrones **3a**–**d**. In most cases the aryl nitrones needed a longer rearrangement time than the alkyl nitrones. The aryl nitrones are less susceptible to rearrangement in comparison to alkyl nitrones. Aryl nitrones (**3e**–**g**) failed to rearrange when heated under reflux in methanol for 20 h (entries 18–20) but **3g** readily rearranged to **4g** in good to excellent yields when heated under reflux in ethanol, acetonitrile or benzene–TsOH (entries 21–23). As with alkyl nitrones, aryl nitrone **3g** also underwent rearrangement to **4g** when stirred in AcOH at room temperature (entry 24).

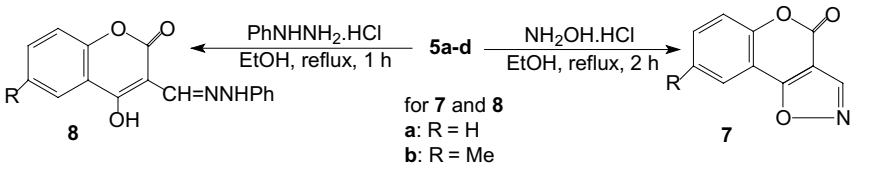
Considering the mechanism for the formation of **4** and **5** from **3** (Scheme 1), it is observed that, during formation of **4**, the pyran ring opens to form **6** (Scheme 1, path a) followed by a 1,5-H-shift. This route is facilitated by the polarity of the solvent. In contrast, formation of **5** requires a tandem electrocyclic ring closure and a 1,5-H shift (Scheme 1, path b), both of which are thermally allowed processes.

The above experiments enabled us to synthesize **4** (R′ = alkyl) or **5** (R′ = alkyl) selectively from **3** (R′ = alkyl). Compound **5** (R′ = alkyl) having a β-alkylamino-α,β-unsaturated ketone moiety produced coumarino[3,4-*d*] isoxazole **7**[9] in quantitative yield when heated with hydroxylamine hydrochloride in ethanol at reflux for 2 h. Similar treatment of **5** (R′ = alkyl) with phenylhydrazine hydrochloride produced the hydrazone derivative **8** (Scheme 2).

From these reactions, the β-alkylamino-α,β-unsaturated ketone **5** (R′ = alkyl) may be considered as a synthetic equivalent of the versatile substrate 4-hydroxy-3-form-



Scheme 1.



Scheme 2.

ylcoumarin. It should be mentioned that 3-(*N*,*N*-dialkylaminomethylene)-4-chromanone **5** (NR_2 in place of NHR′ and CH_2 in place of the C=O at the 2-position) undergoes a similar reaction only when the enamines are derived from 2°-amines, but fails to react when the enamines are derived from 1°-amines.[4c] Intramolecular H-bonding in the latter compound was assumed to be responsible for the failure.[4c] However, in the present case, **5** (R′ = alkyl) undergoes such reactions readily despite the 1°-nature of the amine from which the enamine **5** (R′ = alkyl) is formed. This may be due to the presence of another carbonyl function at the 2-position, which is engaged in H-bonding and keeps the other carbonyl function free to react.

In conclusion, we have synthesized **4** (R′ = alkyl/aryl) in excellent yield compared to earlier reports[2c,5] by modifying the solvent for the rearrangement of **3**. A synthetic route to hitherto unreported 3-(alkylaminomethylene)chroman-2,4-diones **5** (R′ = alkyl) with moderate yields has been revealed and those compounds have been shown to be the synthetic equivalents of the versatile substrate 3-formyl-4-hydroxycoumarin.

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7. **5b**: White solid, ν_{max} (KBr): 3450, 3244, 2977, 1695, 1637, 1618, 1579 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 11.95 (br s, 1H, NH, *Z*), 10.25 (br s, 1H, NH, *E*), 8.57 (d, $J = 14.9$ Hz, 1H, –CH, *E*), 8.41 (d, $J = 14.1$ Hz, 1H, –CH, *Z*), 7.89 (d, $J = 1.9$ Hz, 1H, 5H, *E*), 7.80 (d, $J = 2.0$ Hz, 1H, 5H, *Z*), 7.37 (dd, $J = 8.2$, 1.9 Hz, 1H, 7H, *E*), 7.36 (dd, $J = 8.3$, 2.0 Hz, 1H, 7H, *Z*), 7.14 (d, $J = 8.2$ Hz, 1H, 8H, *E*), 7.13 (d, $J = 8.3$ Hz, 1H, 8H, *Z*),

3.68–3.55 (m, 2×2H, N–CH_2Me, *E*+*Z*), 2.40 (s, 2×CH_3, ArCH_3, *E*+*Z*), 1.41 (t, $J = 7.3$ Hz, 2×CH_3, N–CH_2 CH_3, *E*+*Z*); analysis: calculated for ($C_{13}H_{13}NO_3$) C, 67.52; H, 5.67; N, 6.06%. Found C, 67.48; H, 5.65; N, 6.00%.

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