Cinnamoylacetonitrile in Heterocyclic Synthesis, Part 7 [1]. Simple Synthesis of Benzothiazepines, Pyrones and Oxazolopyridine

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Cinnamoylacetonitrile, 2,4-Diarylbenzothiazepines, Dehydrogenation, Tetra-chloro-*o*-benzoquinone, Acylation

A facile synthesis of the entitled compounds is reported starting with cinnamonitrile.

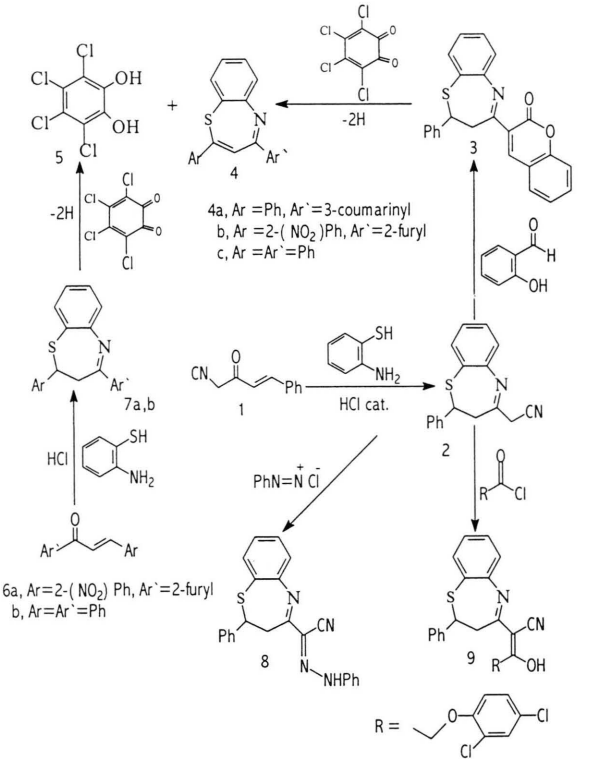
Introduction

Cinnamoylacetonitriles are versatile reagents in organic synthesis, their functional groups are present in a special arrangement which permit simple synthesis of a variety of heterocycles. We have previously reported their utility in the preparation of pyridazines, pyrans, coumarins and condensed heterocycles [1–4]. In the present investigation, we continue our study on cinnamoylacetonitrile aiming to prepare the entitled ring systems.

Results and Discussion

Cinnamoylacetonitrile (**1**) reacted with *o*-aminothiophenol in presence of HCl catalysis to give the 4-cyanoacetyldihydrobenzothiazepine (**2**). It showed an ABX pattern attributable to the benzothiazepine moiety as dds at δ 2.6 , δ 3.0 and δ 4.7 ppm along with the methylene protons singlet at δ 4.5 ppm and a CN absorption at 2200 cm^{-1}. Elemental analysis as well as the mass spectral data showing a molecular formula compatible with $C_{17}H_{14}N_2S$ *m/z* (M^+278) confirmed the given structure together with its chemical behavior.

Thus, compound **2** reacted readily with salicylaldehyde to form the expected coumarin derivative **3** which lacked the CN absorption and a CO one appeared instead at 1700 cm^{-1}. It also revealed coumarin H-4 at δ 8.0 ppm beside the other dihydrobenzothiazepine characteristics. Compound **3** could be easily dehydrogenated at room temperature by tetrachloroquinone to give the corresponding benzothiazepine (**4a**) and tetrachlorocatechol (**5**) [5]. In compound **4a**, the aliphatic ABX system present in **3** disappeared and instead a new aromatic multiplet was detected at δ 7.4–7.8 ppm beside the coumarinyl H-4. Elemental analysis and spectral data were also in full accord.



This simple method of dehydrogenation [6] encouraged us to test its validity on other dihydrobenzothiazepines. So, the propenones **6a,b** were treated with o-aminothiophenol in presence of HCl as a catalyst, similar to (**1**), thus affording the

corresponding dihydrobenzothiazepines (**7a,b**). Compared to the Stephenes procedure [7], this simple modification afforded compounds **7a,b** nearly as sole products. The structure of **7a** was confirmed by analytical, spectral data and analogy [7]. Compounds **7a,b** were then treated with o-tetrachlorobenzoquinone under similar reaction conditions as used for **3**, to afford the aimed dehydro-genated derivatives **4b,c** together with tetrachlorocatechol **5**. Structures **4b,c** were confirmed by elemental and spectral data where their ^{1}H NMR lacked the ABX system, present in **7a** at δ 3.0, δ 3.4 and δ 5.5 ppm. Also, the mass spectrum of **7a** gave a molecular formula $C_{19}H_{14}N_2O_3S$ *m/z* (M^+350) while that of its dehydrogenated derivative **4b** was compatible with $C_{19}H_{12}N_2O_3S$ *m/z* (M^+348).

Compound **2** could be simply diazotized to afford the newly prepared diazo derivative **8**. Meantime, it was acylated readily using 2,4-dichlorophenoxymethyl acid chloride, giving the corresponding acyl derivative **9**.

The structures of **8** and **9,** respectively, were deduced from their analytical and spectral data (*cf.* Tables). Thus, the presence of the cyanomethyl side arm in structure **2** could be utilized to prepare interesting derivatives, capable of further chemical transformations or cyclization reactions.

Continuing our investigation on the utility of cinnamoylacetonitrile in heterocyclic synthesis, it was acylated with 3,4,5-trimethoxyphenyl and 2,4-dichlorophenoxymethyl acid chlorides, respectively, in presence of sodium hydride, affording the 4-pyrone derivatives **10** in satisfactory yield. These compounds showed the pyrone H-5 beside the aromatics of cinnamoacetonitrile (**1**) and those of the acid chloride radical, while their mass spectra gave molecular weights equivalent to the acylated structure minus 2H; these data beside elemental analysis and IR confirmed the structure of **10**. A similar reaction pathway was previously discussed [8].

Furthermore, compound **1**, after nitrosation [9], was treated with Sn/HCOOH (50%). The product

Table I. Physical data for the prepared compounds.

Compd no.	Colour/ Yield%	M. p. [°C] / Solvent of crystallization	Mol.Wt / Mol. Formula	Analysis [%] Calc./Found			
				C	H	N	S
2	50	182	$C_{17}H_{14}N_2S$	73.35	5.07	10.06	11.52
	pale yellow	MeOH	278.364	73.1	4.9	9.7	11.2
3	45	228	$C_{24}H_{17}NO_1S$	75.17	4.47	3.65	8.36
	colourless	dioxane	383.451	75.0	4.2	3.4	8.0
4a	55	192	$C_{24}H_{15}NO_2S$	75.57	3.96	3.67	8.41
	colourless	MeOH	381.431	75.3	3.6	3.3	8.1
4b	30	182	$C_{19}H_{12}N_2O_3S$	65.50	3.47	8.04	9.20
	yellow	MeOH	348.374	65.3	3.3	7.8	8.8
4c	40	150	$C_{21}H_{15}NS$	80.47	4.82	4.47	10.23
	reddish brown	BuOH	313.401	80.3	4.5	4.2	10.0
7a	50	180	$C_{19}H_{14}N_2O_3S$	65.12	4.03	8.00	9.15
	yellow	MeOH	350.384	64.8	4.0	7.8	8.8
8	60	197	$C_{23}H_{18}N_4S$	72.22	4.74	14.65	8.38
	yellow	MeOH	382.464	72.1	4.5	14.3	8.0
9	60	154	$C_{25}H_{18}Cl_2N_2O_2S$	62.37	3.77	5.82	6.66
	pale yellow	MeOH	481.384	62.2	3.5	5.6	6.3
10a	20	134–35	$C_{21}H_{17}NO_5$	69.41	4.72	3.85	–
	yellow	C_6H_6	363.357	69.2	4.5	3.5	–
10b	60	150	$C_{19}H_{11}Cl_2NO_3$	61.31	2.98	3.76	–
	pale yellow	MeOH	372.197	61.1	2.7	3.4	–
11	55	192	$C_{11}H_{10}N_2O$	70.95	5.41	15.05	–
	colourless	MeOH	186.21	70.8	5.3	14.8	–
13	60	220	$C_{12}H_{10}N_2O_2$	67.28	4.70	13.05	–
	pale yellow	MeOH	214.22	67.0	4.4	12.7	–
14	45	264	$C_{12}H_8N_2O_2$	67.91	3.80	13.20	–
	colourless	dioxane	212.204	67.7	3.6	12.9	–

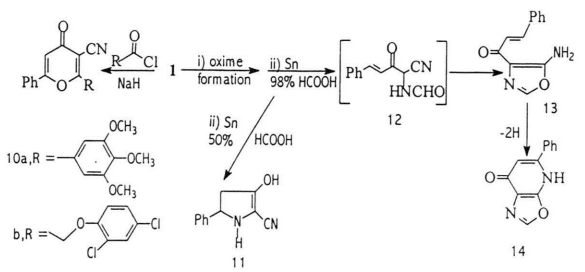
Satisfactory halogen analysis were obtained for compounds **9** and **10b**.

Table II. Spectral data of the newly prepared compounds.

Compd. No.	IR (cm^{-1})	^1H NMR- δ (ppm)
2	2200 (CN), 1620 (C=N)	2.6 (dd, J_{vic} = 10Hz, J_{gem} = 15Hz, 1H, methylene H-axial), 3.0 (dd, J_{vic} = 6Hz, J_{gem} = 15Hz, 1H, methylene H-equatorial), 4.5 (s,2H,CH_2CN), 4.7 (dd, J_{vic1} = 10Hz, J_{vic2} = 6Hz, 1H,methine H), 7.0–7.5 (m,9H,C_6H_5 and benzothiazepine H-6 to H-9).
3	1700 (CO)	2.4 (dd,J_{vic} = 10Hz, J_{gem} = 15Hz, 1H, methylene H-axial), 3.1 (dd,J_{vic} = 6Hz,J_{gem} = 15Hz, 1H, methylene H-equatorial), 4.4 (dd, J_{vic1} = 10Hz, J_{vic2} = 6Hz, 1H, methine H), 6.7–7.6 (m, 13H, C_6H_5, benzothiazepine H-6 to H-9 and coumarin H-5 to H-8), 8.0 (s, 1H, coumarin H-4).
4a	———	7.4–7.8 (m, 14H, C_6H_5, coumarin H-5 to H-8, benzothiazepine H-3 and H-6 to H-9), 8.1 (s,1H, coumarin H-4).
4b	———	6.6–6.8 (m, 2H, furan H-4, H-3), 7.0–8.1 (m, 10H, C_6H_4, benzothiazepine H-3 , H-6 to H-9 and furan H-5).
4c	———	6.9–8.0 (m, 15H, $2C_6H_5$, benzothiazepine H-3, H-6 to H-9).
7a	1640 (C=N)	3.0 (dd, J_{vic}= 10Hz, J_{gem} = 15Hz, 1H, methylene H-axial), 3.4 (dd,J_{vic}= 6Hz, J_{gem}= 15Hz, 1H, methylene H equatorial), 5.5 (dd, J_{vic1} = 10Hz, J_{vic2} = 6Hz, 1H, methine H), 6.7 (dd, 1H, furanH-4), 7.1–8.0 (m, 10H, C_6H_4, benzothiazepine, H-6 to H-9, furan H-3 and H-5).
8	3100–2800 (NH and ring stretching), 2200 (CN)	2.7 (dd, J_{vic} = 10Hz, J_{gem} = 15Hz, 1H, methylene H-axial), 3.2 (dd,J_{vic} = 6Hz, J_{gem} = 15Hz, 1H, methylene H-equatorial), 5.1 (dd, J_{vic1}= 10Hz, J_{vic2} = 6Hz, 1H, methine H), 7.2–7.6 (m,14H,$2C_6H_5$ and benzo-thiazepine H-6 to H-9), 14.6 (s,1H,NH).
9	2200 (CN), 1650 (CO)	2.9 (dd, J_{vic} = 10Hz, J_{gem} = 15Hz, 1H, methylene H-axial), 3.1 (dd, J_{vic} = 6Hz, J_{gem} = 15Hz, 1H, methylene H-equatorial), 4.9 (dd, J_{vic1} = 10Hz, J_{vic2} = 6Hz, 1H, methine H), 5.4 (s, 2H, phenoxy-methylene), 7.1–7.7 (m, 12H, benzothiazepine H-6 to H-9,C_6H_5 and C_6H_3), 12.4 (s,1H ,OH).
10a	2200 (CN), 1685 (CO)	3.7–3.8 (2s,9H, $3OCH_3$), 7.1 (s,2H,C_6H_2), 7.3–7.6 (m,6H,C_6H_5 and pyron H-5).
10b	2200 (CN), 1680 (CO)	5.4 (s, 2H, phenoxy CH_2), 7.4–7.7 (m, 9H, C_6H_5, C_6H_3 and pyron H-5).
11	3100–2800 (NH and OH), 2200 (CN)	3.2 (m, 2H, pyrrolidine CH_2), 5.1 (s, 1H, NH), 6.1(m, 1H, pyrrolidine H-5), 7.4–7.6 (m,5H, C_6H_5), 8.5 (s, 1H,OH).
13	3400–3200 (NH_2), 1710 (CO)	7.2 (d, J = 15H, 1H, olefinic H-1), 7.4–7.6 (m,5H, C_6H_5), 8.0 (d, J = 15Hz, 1H, olefinic H-2), 8.7 (s, 1H, oxazole H-2).
14	3300 (NH), 1690 (CO)	7.4–7.6 (m, 5H, C_6H_5), 8.2 (s,1H, oxazolopyridine H-2), 8.4 (s, 1H, oxazolopyridine H-5), 11.6 (s,1H, NH).

obtained gave a molecular formula $C_{11}H_{10}N_2O$ *m/z* (M^+186); it showed OH, CN and NH absorptions together with two signals at δ 3.2 (2H) and δ 6.1 (1H) ppm. Accordingly, the pyrrolidinone structure of **11** was assigned to this product.

When the same reaction was repeated using 98% HCOOH instead of 50%, a different product



was obtained with a molecular formula $C_{12}H_{10}N_2O_2$ *m/z* (M^+214). It lacked the CN absorption, detected in the parent oxime, and showed CO and NH_2 absorptions at 1710 and 3400–3200 cm^{-1}. While its ^1H NMR revealed two doublets at δ 7.2 and δ 8.0 ppm, similar to those present in the parent oxime and attributed to the olefinic protons. So, the cinnamoyloxazole structure **13** was given to this product. This could be explained *via* initial reduction to form the 2-aminopentenenitrile, followed by its formylation to afford the intermediate **12** which undergoes intracyclization *via* its enol form and the CN group to the final isolable product **13**. While in presence of 50% HCOOH, the reduction step is followed by intracyclization (NH_2 group and olefinic double bond) to form **11**. The structure of **13** was also

confirmed chemically: it was refluxed in dioxane affording a new compound for which structure **14** was given, based on analytical and spectral data. Thus, it showed the pyridooxazole H-2 and H-5 at δ 8.2 and δ 8.4 ppm, respectively, and its mass spectral data are also in full accord.

Experimental

Melting points are uncorrected and were taken on Electrothermal 9100 apparatus. IR spectra were recorded on Carl Zeiss spectrophotometer instrument model "UR 10" using KBr. ^{1}H NMR spectra were determined on a Jeol 270 MHz instrument using tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a Finigan SSQ 7000 mass spectrometer. Microanalysis were performed by the Central Service Laboratory at Cairo University.

2,4-Disubstituted-2,3-H-benzothiazepines (**2**) *and* (**7a,b**)

Each of compounds **1**, (**6a,b**) (0.01 mole) was refluxed with *o*-aminothiophenol (0.01 mole, 1.25 g) in methanol (30 ml) for 10 minutes. Then, conc HCl (5 drops) was added and the solution cooled. The precipitate formed was collected and crystallized.

4-(3-Coumarinyl)-2-phenyl-2,3-H-benzothiazepine (**3**)

A mixture of **2** (0.01 mole, 2.89 g) with an equimolar amount of salicylaldehyde was refluxed in methanol (30 ml) in presence of piperidine (3 drops) for 6 h. After partial concentration, the precipitate obtained was collected and crystallized.

2,4-Diarylbenzothiazepines (**4a-c**)

Tetrachloro-*o*-benzoquinone (0.01 mole, 2.45 g) was added while stirring at room temperature to a solution of each of benzothiazepines (**2**), (**7a,b**), (0.01 mole) in dry ether (100 ml). After few hours, the separated solid was collected by filtration, washed with ether, dried and recrystallized. The original ethereal mother liquor was extracted with a 10% aqueous sodium hydroxide solution, the extract acidified with cold dilute HCl, and the precipitate obtained proved to be tetrachlorocatechol (m.p. and mixed m.p. of its diacetate derivative, 184° [5]).

2-Phenyl-4-[1-(phenyldiazo)cyanomethyl]-2,3-H-benzothiazepine (**8**)

The phenyl diazonuim chloride was added to a cooled mixture of (2) (0.01 mole, 2.78 g) and sodium acetate trihydrate (5 g) in dimethylformamide (30 ml) with stirring for 30 min; water was then added and the precipitate was filtered off and crystallized.

2-Phenyl-4-(3-hydroxy-3–2,4-dichlorophenoxymethylacrylonitrile-2-yl)-2,3-H-benzothiazepine (**9**) *and 2-aryl-3-cyano-6-phenylpyran-4ones* (**10a,b**)

To a solution of each of compounds **1** or **2** (0.01 mole) in dry tetrahydrofuran (20 ml) in presence of sodium hydride (0.01 mole) at room temperature (25 °C), a solution of the appropriate acid chloride (0.01 mole) in dry tetrahydrofuran (10 ml) was dropped over with stirring for ½ h, then the salt formed was filtered off and the organic layer was treated with 1 ml 50% HCl and partially concentrated. The precipitate, thus formed, was collected and crystallized.

2-Cyano-5-phenylpyrrolidin-3-one (**11**) *and 5-amino-4-cinnamoyloxazole* (**13**)

Compound **1** was nitrosated to prepare the oximinocinnamoylacetonitrile as reported [9]. Then, to the oxime (0.01 mole, 2.0 g) in 50% or 98% formic acid (30 ml), Sn (0.01 mole, 1.2 g) was added portionwise at 60 °C over ½ h and stirring was kept for further 6 h at the same temperature. The solution was then left overnight at room temperature. A precipitate was formed and found to be a mixture of the product with inorganic residuals. So, it was boiled in methanol, filtered while hot and the filtrate was cooled and left to precipitate. The product obtained was then filtered off and crystallized.

4-Oxo-6-phenyloxazolo[4,5-b]pyridine (**14**)

Compound **13** (0.01 mole, 2.14 g) was refluxed in dioxane (25 ml) for 6 h. The solution was partially concentrated and the precipitate collected and crystallized.

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