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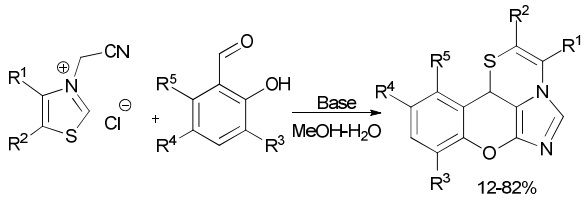

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ARTICLE

Domino reaction of *N*-(cyanomethyl)-1,3-azolium quaternary salts with *o*-hydroxybenzaldehydes: Scope and limitations

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A route towards chromenes, annulated with an imidazo[5,1-*c*][1,4]thiazine core through a base-promoted domino reaction of thiazolium quaternary salts, has been developed. The synthesised compounds show high cytotoxic activity against human tumour cell lines.

Introduction

Domino reactions, also known as tandem or cascade reactions, have emerged as a highly effective strategy for the synthesis of heterocyclic compounds, including bioactive natural products and pharmaceutical agents.[1] These protocols enable chemists to perform complex synthetic conversions with high efficiency using readily available starting materials, often via a biomimetic pathway.[2] Thus, domino reactions contribute exceedingly to synthetic drug design strategies, enhance elegant approaches in total synthesis and improve yields in large-scale syntheses.[1,2] The advantages of these methods include excellent atom economy, high selectivity and less waste.[3] Additionally, using these strategies, multiple transformations can be carried out in a single laboratory operation without the isolation of intermediates, making them prime examples of green chemistry.[4] Despite the widespread proliferation of domino reactions, researchers have continued to channel their efforts in this area, as new heterocyclic structures and novel substitution patterns are required.[5]

The reactivity of *N*-(cyanomethyl) heterocyclic quaternary salts in domino reactions are of interest, owing to the structural complexity generated and the potential biological activity of the resulting products. Investigations in this field have shown the possibility to easily transform pyridinium salts to chromenoimidazopyridines,[6] isoquinolinium salts to chromeno-[7] and thiochromeno-imidazoisoquinolines.[8] Moreover, we have had preliminary results showing a route to the chromenoimidazothiazine core through the ANRORC transformation of *N*-(cyanomethyl)-1,3-thiazolium salts under the action of salicylic aldehydes.[9] The optimisation of the latter reaction conditions, the extension of the methodology to other 1,3-azoles and the biological evaluation of the chromeno-imidazothiazines are disclosed in the present paper.

Results and discussion

Synthesis of *N*-(cyanomethyl)-1,3-azolium salts

The preparation of the starting thiazolium salts, **1a–c**, has previously been reported.[9] The yields can be significantly increased by running the reactions under microwave (MW) irradiation conditions (Table 1). Imidazolium salt **2** was prepared with a good yield without employing MW irradiation. Unfortunately, we did not succeed in preparing the oxazolium quaternary salts by any means; the use of more facile leaving groups (–Br, –I), solvent-free techniques and MW irradiation did not provide positive results.

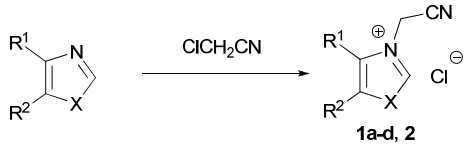


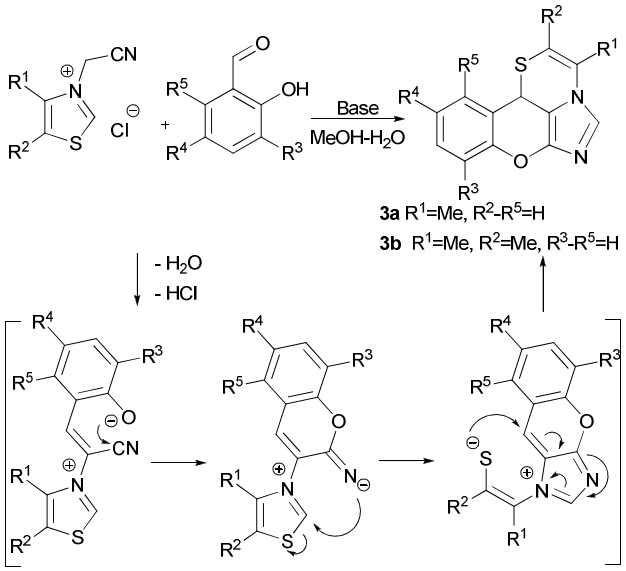
Table 1. The synthesis of quaternary salts **1**, **2**.

Product	R^1	R^2	X	Conditions	Prev. Rep. Yield, %	Yield, %
1a	H	H	S	MW, 140°C, 30 min, solvent-free	49	81
1b	Me	H	S	MW, 140°C, 30 min, solvent-free	33	79
1c	Me	Me	S	MW, 140°C, 30 min, solvent-free	20	82
1d	H	Me	S	MW, 140°C, 30 min, solvent-free	65	81
2	H	H	N-	CH_3CN,	-	78

Me	50°C, 1 h	

Reaction of thiazolium salts with *o*-hydroxybenzaldehydes: Optimisation and scope

Owing to preliminary studies,[9] the reaction of thiazolium salts **1** with *o*-hydroxybenzaldehydes under base-promoted conditions proceeded as a domino process, involving an ANRORC step, and led to the formation of chromenoimidazothiazines **3** (Scheme 1).



Scheme 1. Plausible scheme of chromenoimidazothiazine formation.

The initial optimisation of the reaction conditions showed that the use of 20 mol% sodium carbonate as a base and MeOH–H_2O as a solvent was optimal. Still, the yields of the tetracyclic products were satisfactory, but the reaction failed to produce target compounds with salicylic aldehyde (R^3, R^4, R^5=H). To overcome these problems, a more thorough study of the reaction conditions was initiated. The reactions of thiazolium salts **1b** and **1c** with salicylic aldehyde were chosen as the model, and the results of the optimisation process are summarised in Table 2. It has been shown that the use of promoters such as ammonium acetate, potassium *tert*-butoxide, L-proline, triethylamine or dimethylaminopyridine resulted in the formation of only trace amounts of products **3a** and **3b** (Table 2, entries 1–6). The use of potassium carbonate (20 mol%) provided compound **3b** in 18% yield in refluxing MeOH–H_2O for 3 h. The use of 60 mol% K_2CO_3 raised the yield to 38% with 3 h reflux. A further increase in the amount of K_2CO_3 (100 mol%) provided compound **3b** in 48% yield after 10 min reflux, but resulted in complex-mixture formation in the case of **3a** (Table 2, entries 10 and 11). The employment of TFE or DMF as solvents did not result in any yield improvements (Table 2, entries 13–15). DBU was found to be the most suitable base, as compound **3b** was obtained in 61% yield and **3a** in 62% yield. Further studies failed to improve these yields. The methanol and water were not used separately due to the poor solubility of the quaternary salts in pure alcohol and substituted aldehydes in pure water. As far as the products of the reactions precipitate from the reaction mixture, the homogeneity of the starting reactants in the solvent is important for producing the precipitates with the acceptable purity. The general recommendations for carrying out these reactions are the avoidance of high temperatures and to minimise the reaction time when using either an equivalent or excess amount of base.

Table 2. Optimisation of the model reaction conditions.

Entry	T, °C	t, h	Solvent	Promoter	Prod.	Yield, %
1	reflux	1	MeOH-H_2O	NH_4OAc (100 mol%)	**3b**	10
2	reflux	3	MeOH-H_2O-THF	*t*-BuOK (20 mol%)	**3a**	trace
3	r.t.	12	MeOH-H_2O	L-Proline (10 mol%)	**3a**	trace
4	reflux	3	MeOH-H_2O	L-Proline (120 mol%)	**3a**	trace
5	r.t.	3	MeOH-H_2O	Et_3N (100 mol%)	**3a**	7
6	reflux	3	MeOH-H_2O	DMAP (100 mol%)	**3a**	trace
7	reflux	3	MeOH-H_2O	K_2CO_3 (20 mol%)	**3b**	18
8	reflux	1	MeOH-H_2O	K_2CO_3 (20 mol%)	**3a**	19
9	reflux	3	MeOH-H_2O	K_2CO_3 (60 mol%)	**3b**	38
10	reflux	0.1	MeOH-H_2O	K_2CO_3 (100 mol%)	**3b**	48
11	reflux	0.1	MeOH-H_2O	K_2CO_3 (100 mol%)	**3a**	trace
12	40	1	MeOH-H_2O	K_2CO_3 (100 mol%)	**3a**	37
13	80	1	DMF	K_2CO_3 (20 mol%)	**3a**	trace
14	80	1	DMF	K_2CO_3 (100 mol%)	**3a**	trace
15	reflux	0.1	TFE	K_2CO_3 (100 mol%)	**3a**	10
16	reflux	1	MeOH-H_2O	DBU (100 mol%)	**3b**	43
17	r.t.	18	MeOH-H_2O	DBU (110 mol%)	**3b**	61
18	r.t	18	MeOH-H_2O	DBU (110 mol%)	**3a**	62

To show the advantages of the newly selected conditions, previously reported compounds were obtained by a modified protocol. Thus, the yields of compounds **3d**, **3e**, **3g** and **3h** were significantly improved (Table 3, entries 4–7 and 9–12). The reaction worked well for aldehydes bearing both electron-donating and electron-withdrawing groups, giving target compounds **3** with satisfactory-to-good yields (Table 3).

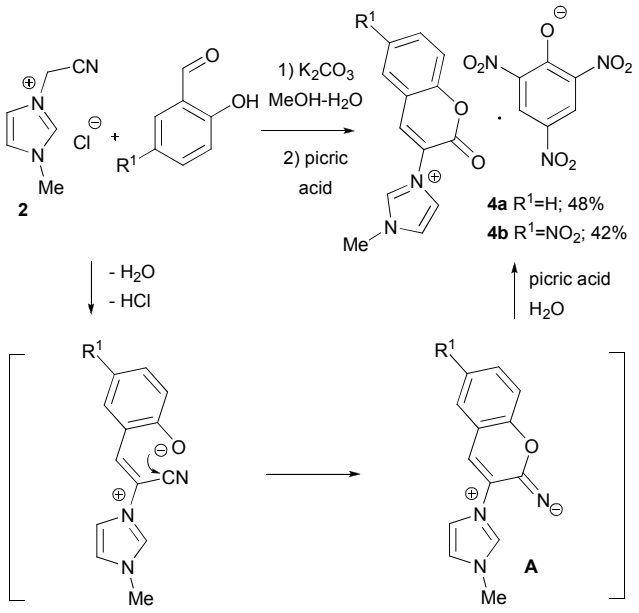
Reactions of imidazolium salt with *o*-hydroxybenzaldehydes

The reactions of imidazolium salt **2** with *o*-hydroxybenzaldehydes were anticipated to proceed in a similar way. Despite the expectations, the reaction of **2** and salicylic aldehyde in MeOH–H_2O, using K_2CO_3 as a base, produced no mobile spots on the TLC plate. The resulting product **4a** precipitated from the reaction mixture after the addition of

Table 3. The scope of chromenoimidazothiazines **3**.

Entry	R^1	R^2	R^3	R^4	R^5	Conditions	Product	Yield, %
1	Me	H	H	H	H	DBU (110 mol%), r.t., 18 h	**3a**	62
2	Me	Me	H	H	H	DBU (110 mol%), r.t., 18 h	**3b**	61
3	H	Me	H	H	H	K_2CO_3 (110 mol%), 40 °C, 1h	**3c**	34
4	Me	H	H	Br	H	Na_2CO_3 (20 mol%), reflux, 1h	**3d**	28
5	Me	H	H	Br	H	DBU (110 mol%), r.t., 18 h	**3d**	61
6	Me	Me	H	Br	H	Na_2CO_3 (20 mol%), reflux, 1h	**3e**	12
7	Me	Me	H	Br	H	DBU (110 mol%), r.t., 18 h	**3e**	61
8	H	Me	H	Br	H	DBU (110 mol%), r.t., 12 h	**3f**	46
9	Me	H	H	NO_2	H	Na_2CO_3 (20 mol%), reflux, 1h	**3g**	27
10	Me	H	H	NO_2	H	DBU (110 mol%), r.t., 18 h	**3g**	81
11	Me	Me	H	NO_2	H	Na_2CO_3 (20 mol%), reflux, 1h	**3h**	12
12	Me	Me	H	NO_2	H	DBU (110 mol%), r.t., 18 h	**3h**	76
13	H	Me	H	NO_2	H	DBU (110 mol%), r.t., 12 h	**3i**	34
14	Me	Me	H	-CH-(CH)$_2$-CH-		K_2CO_3 (20 mol%), reflux, 45 min	**3j**	30
15	H	Me	H	-CH-(CH)$_2$-CH-		K_2CO_3 (20 mol%), reflux, 45 min	**3k**	37
16	Me	H	H	OMe	H	K_2CO_3 (110 mol%), 40 °C, 1h	**3l**	54
17	Me	Me	H	OMe	H	K_2CO_3 (110 mol%), 40 °C, 1h	**3m**	72
18	H	Me	H	OMe	H	K_2CO_3 (110 mol%), 40 °C, 1h	**3n**	58
19	Me	Me	OMe	NO_2	H	DBU (110 mol%), r.t., 18 h	**3o**	43

picric acid, making it possible to characterise the products by X-ray analysis.[10] The formation of this coumaryl-substituted imidazolium picrate may be explained by the hydrolysis of the 42% yield. To avoid hydrolysis, the reaction was carried out in water-free conditions, but the exploitation of dry DMF or MeOH led to the formation of inseparable mixtures.

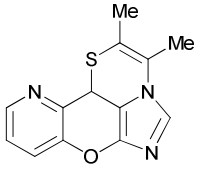


Scheme 2. Coumaryl-substituted imidazolium picrate **4** formation.

Biological evaluation of chromenoimidazothiazines

Compounds **3b, 3e, 3l, 3m** and **5**[9] were evaluated *in vitro* for their cytotoxic activity against four human tumour cell lines (KB, Hep-G_2, LU and MCF-7), and the results are summarised in Table 4. These particular compounds have been selected due to their better water solubility. Four chromeno-imidazothiazine derivatives showed strong activity against the KB cell line with an IC_{50} value below 100 µg/mL. Analogues **3m** and **3l** exhibited potent cytotoxicity against the KB cell line with IC_{50} = 4 and 6.32 µg/mL, respectively. Meanwhile, analoguess **3e** and **3l** inhibited the Hep-G_2 cell line with IC_{50} values in the 80–117.5 µg/mL range. Derivative **3m** displayed cytotoxic activity against LU cell lines, with an IC_{50} value of 99.76 µg/mL. Concerning the last cell line, MCF7, the chromenoimidazothiazines analogues showed weak activities, with IC_{50} values above 128 µg/mL. It is noteworthy to mention that two derivatives, **3m** and **3l**, present a cytotoxicity activity against the cancer cell line KB that is comparable with ellipticine.

Table 4. Cytotoxic activity of compounds **3b**, **3e**, **3l**, **3m** and **5**.

Compound	Cell line, IC_{50} µg/mL			
	KB	**HepG_2**	**Lu**	**MCF-7**
Ellipticin	**0.25**	**0.29**	**1.18**	**0.71**
3b	**32**	>128	>128	>128
3e	**68.0**	**117.5**	>128	> 128
3l	**4**	**80**	>128	>128
3m	**6.32**	>128	**99.76**	>128
 **5**	> 128	> 128	> 128	> 128

Conclusions

A number of 10*bH*-6-oxa-1-thia-3*a*,5-diazaacephenanthrylenes have been synthesised through the ANRORC domino reaction of *N*-(cyanomethyl)-1,3-thiazolium salts with salicylic aldehydes. It has been shown that 3-(cyanomethyl)-1-

methylimidazolium chloride reacts with salicylic aldehydes differently to expected, forming coumaryl-substituted imidazolium salts. It has been also reported that the 1,3-oxazole failed to give the *N*-cyanomethyl quaternary salt. Some of the synthesised compounds were tested *in vitro* and showed high cytotoxic activity against human tumour cells.

Acknowledgements

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Notes and references

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Electronic Supplementary Information (ESI) available: experimental procedures, copies of ^{1}H and ^{13}C spectra. See DOI: 10.1039/b000000x/

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