Pergamon

Tetrahedron Letters 42 (2001) 2553–2555

TETRAHEDRON LETTERS

Novel and convenient synthesis of polyfunctionalized quinolines, quinolones and their annulation reactions

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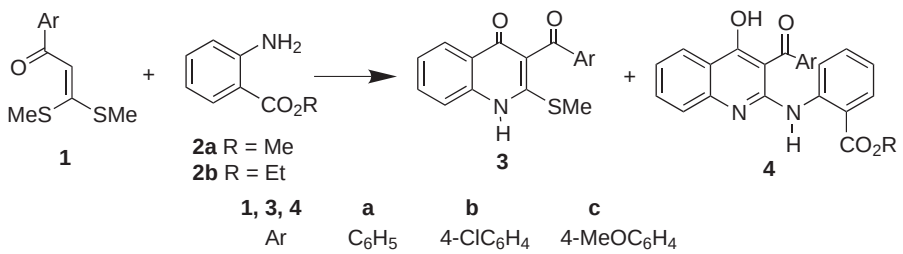
Received 11 December 2000; revised 26 January 2001; accepted 7 February 2001

Abstract—The reaction of α-aroylketene dithioacetals with esters of *o*-aminobenzoic acid under different conditions afforded preferentially 2-methylthio-3-aroylquinolones and 2-anilino-3-aroylquinolines through, respectively, α-aroylketene *N*,*S*-acetal and α-aroylketene aminal intermediates. The annulation reaction of 2-methylthio-3-aroylquinolones with hydrazine gave both pyrazolo[3,4-*b*]quinolone and pyrazolo[4,3-*c*]quinoline, the selectivity being determined by the reaction conditions employed. Intramolecular cyclocondensation of 2-anilino-3-aroylquinolines produced quino[2,1-*b*]quinazolines in high yield.

Quinoline and quinolone derivatives are very important organic compounds because they occur widely in nature and possess interesting biological and pharmacological activities.[1] Synthetic fluoroquinolones such as norfloxacin and ciprofloxacin, for example, have been used clinically as orally active antibiotics. Currently, there is a renaissance of interest in searching for novel and potent antibacterial agents due to a dramatic and alarming increase in the incidence of bacterial infections resistant to most common antibiotics including fluoroquinolones.[2] Although many preparative methods are available in the literature,[1] it is still challenging to explore new and simple synthetic methods for quinolines and quinolones, particularly for the highly functionalized ones.[3]

α-Oxoketene dithioacetals are versatile intermediates in organic synthesis.[4] They have been extensively used as an electrophilic three-carbon segment in the construction of various five- and six-membered heterocycles.[4] The reaction of α-oxoketene dithioacetals with amines or diamines, however, yielded α-oxoketene *N*,*S*-acetals or (heterocyclic) ketene aminals.[5] Previous studies have shown that ketene aminals[5] and ketene *N*,*S*-acetals[6] are excellent carbon nucleophiles able to react with a wide variety of electrophiles. We therefore envisaged that a tandem reaction comprising the formation of ketene aminals between α-aroylketene dithioacetals[7] and *o*-aminobenzoic acid esters followed by an intramolecular enaminic cyclization would furnish quinolines or quinolones. The resulting multi-functionalized com-



Scheme 1.

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0040-4039/01/$ - see front matter
PII: S0040-4039(01)00231-3

pounds would serve as useful intermediates for further chemical manipulations. Herein, we wish to report a novel and very convenient synthesis of highly functionalized quinoline and quinolone derivatives, and also to demonstrate their potential in the preparation of quinoline- and quinolone-fused heterocycles.

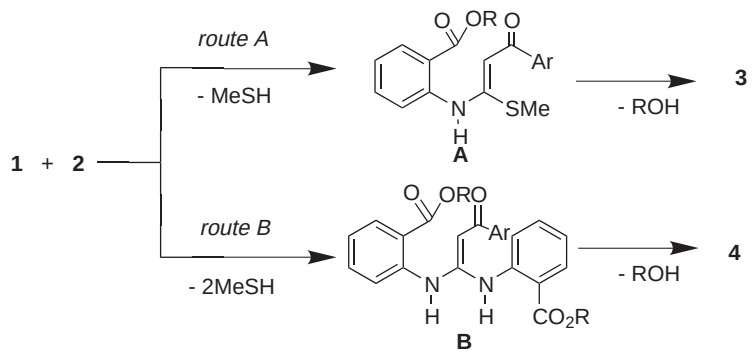
No reaction was observed when α-benzoylketene dithioacetal **1a** was refluxed with methyl *o*-aminobenzoate **2a** in toluene or in DMF. The addition of a strong base such as NaH did not help the reaction either. Only when the reaction was performed in refluxing acetic acid did the reaction proceed smoothly to give a mixture of methylthio-substituted quinolone **3a** and anilino-substituted 4-hydroxyquinoline **4a** (Scheme 1). When 2.5 equivalents of **2** were used, the reaction gave **4** as the major product. Selective formation of **4** was also effected in some cases when a neat reaction between **1** and **2** was heated at an elevated temperature. Interestingly, when a mixture of equal equivalents of **1** and **2** was refluxed in propionic acid, compound **3** was isolated predominantly in moderate yield (Table 1). It should be noted that no reaction took place under the identical conditions between **3** and methyl *o*-aminobenzoate **2a**, suggesting that ketene *N*,*S*-acetal intermediate **A** and ketene aminal intermediate **B** are responsible, respectively, for the formation of **3** and **4** (Scheme 2).

Quinolones **3** are highly functionalized compounds and they are useful intermediates in synthesis. Assembling methylthio, secondary amino and aroyl groups into a molecule, 3-aroyl-2-methylthio-4-quinolone **3** can be viewed as a *pseudo*-α-oxoketene *N*,*S*-acetal. Both the substituents 2-methylthio and 3-aroyl substituents could be reactive towards nucleophiles and therefore **3** could serve as a new electrophilic three-carbon unit. It was envisaged that fused five- and six-membered heterocycles would result from treatment of **3** with appropriate bis-nucleophiles. Reaction between **3** and hydrazine, for instance, afforded hydrazone **5** in almost quantitative yield. Interestingly, however, a mixture of compounds **6**[8] and **7** was obtained by further heating of

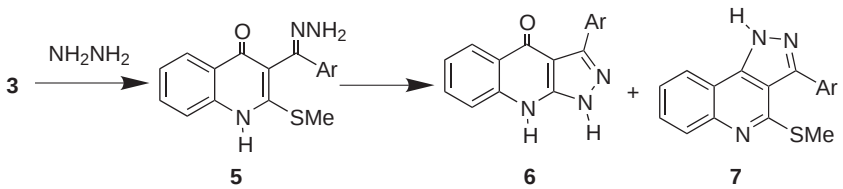
Table 1. Reaction of α-aroylketene dithioacetals **1** with *o*-aminobenzoic acid esters **2**

Entry	1	2	1:2	Reaction conditions	3 (%[a])	4 (%[a])
1	**1a**	**2a**	1:2	CH_3CO_2H, reflux 12 h	31	34
2	**1a**	**2b**	1:1.5	CH_3CO_2H, reflux 20 h	17	23
3	**1a**	**2b**	1:2.5	CH_3CO_2H, reflux 20 h	6	42
4	**1b**	**2b**	1:2.5	CH_3CO_2H, reflux 24 h	12	54
5	**1c**	**2b**	1:2.5	CH_3CO_2H, reflux 24 h	7	74
6	**1b**	**2b**	1:2.4	Neat, Ar, 180°C, 20 h	6	59
7	**1c**	**2b**	1:2.4	Neat, Ar, 180°C, 20 h	5	80
8	**1a**	**2a**	1:1.1	$C_2H_5CO_2H$, reflux 5 days	46	2
9	**1b**	**2a**	1:1.1	$C_2H_5CO_2H$, reflux 5 days	28	Trace
10	**1c**	**2a**	1:1.1	$C_2H_5CO_2H$, reflux 5 days	32	Trace

[a] Isolated yield.



Scheme 2.

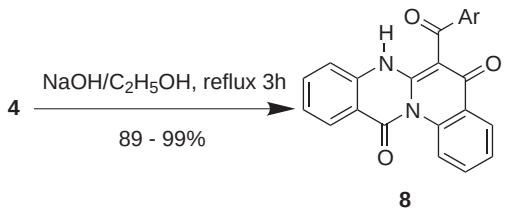


Scheme 3.

Table 2. Selective annulation reaction of hydrazone **5**

Entry	5	Reaction conditions	6 (%)[b]	7 (%)[b]
1	**5a**	Pyridine, Ar, reflux 60 h	70	5
2	**5b**	Pyridine, Ar, reflux 60 h	69	4
3	**5c**	Pyridine, Ar, reflux 60 h	76	9
4	**5a**	Resin,[a] EtOH, reflux 18 h	28	52
5	**5b**	Resin,[a] EtOH, reflux 24 h	18	54
6	**5b**	Resin,[a] CH_3CN/DMF, reflux 32 h	17	56
7	**5c**	Resin,[a] EtOH, reflux 32 h	18	42
8	**5c**	Resin,[a] CH_3CN/DMF, reflux 32 h	24	52

[a] Ion exchange resin Amberlyst-732.
[b] Isolated yield.



Scheme 4.

5 (Scheme 3). Apparently, they were formed from cyclocondensation reactions of the hydrazone with either 2-methylthiol or with quinolone carbonyl groups. Selective synthesis of linear fused heterocycles **6**, or angular fused heterocycles **7**, was readily effected by carrying out the reaction in refluxing pyridine or in the presence the of the ion exchange resin, Amberlyst-732, respectively (Table 2).

Attempts to prepare quino[2,1-*b*]quinazoline **8** through intramolecular cyclization of **4** met with failure under various reaction conditions. Only when heated in ethanolic NaOH solution did cyclization of **4** proceed efficiently to produce **8** in excellent yield (Scheme 4).

In summary, we have provided novel and simple methods for the preparation of functionalized quinolone and quinoline compounds, and demonstrated their usefulness in the synthesis of fused heterocycles. The reaction of α-aroylketene dithioacetals with esters of *o*-aminobenzoic acid under different conditions can afford preferentially 2-methylthio-3-aroylquinolones and 2-anilino-3-aroyl quinolines through, respectively, α-aroylketene *N*,*S*-acetal and α-aroylketene aminal intermediates. Annulation reaction of 2-methylthio-3-aroylquinolones with hydrazine gave both pyrazolo-[3,4-*b*]quinolone and pyrazolo[4,3-*c*]quinoline, the selectivity being determined by the reaction conditions employed. Intramolecular cyclocondensation of 2-anilino-3-aroylquinolines produced quino[2,1-*b*]quinazolines in high yield.

Acknowledgements

We thank the National Natural Science Foundation of China and the Chinese Academy of Sciences for financial support.

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