Tetrahedron Letters 53 (2012) 3242–3244

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Rapid, clean and efficient one-pot synthesis of thiopyrano[2,3-*b*]quinolines via domino Michael addition/cyclization reactions

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ARTICLE INFO

Article history:
Received 18 January 2012
Revised 5 April 2012
Accepted 6 April 2012
Available online 14 April 2012

Keywords:
Domino reaction
Michael addition/cyclization
3-Formyl-quinoline-2-thiones
Thiopyrano[2,3-*b*]quinolines
Et_3N

ABSTRACT

Rapid and efficient one-pot synthesis of thiopyrano[2,3-*b*]quinolines is described from the reaction of 3-formyl-quinoline-2-thiones with acrylonitrile using economical organic base Et_3N at room temperature. The reaction proceeded smoothly via domino Michael addition/cyclization reactions and did not require dry solvent, inert atmosphere and column chromatography purifications.

The importance of quinoline and its annelated derivatives is well recognized by synthetic and biological chemists. Compounds possessing this ring system have wide applications as drugs, pharmaceuticals and agrochemicals.[1] Similarly, the chemistry of thiopyrans has been much less explored than that of the analogous pyrans. Recently, interest in the sulfur-heterocycles has significantly increased since a wide range of biological activities associated with the scaffold have been identified. Amongst the thiopyran fused heterocycles, thiopyranoquinoline containing both quinoline ring and thiopyran moieties, have afforded unique biological activities, for example, thiopyrano[2,3-*c*]quinoline, MT477 is reported as a potential anticancer drug with a high activity against protein kinase C (PKC) isoforms[2] and inspite of these thiopyran moieties also exhibited anti-inflammatory, anti-bacterial, anti-microbial, anti-hyperplasia, antipsychiatric, analgesic and anti-cancer activities.[3,6] Thus, the development of facile synthetic strategies to access such heterocycles is always of considerable interest.

Consequently, several syntheses have been developed for thiopyrans.[4] Multicomponent and microwave assisted reactions are amongst the most useful routes for the synthesis of these compounds. Recently, multicomponent reactions involving aromatic aldehydes, naphthalen-2-amine and tetrahydrothiopyran-4-one to the synthesis of thiopyran fused-quinolines have been reported by Wang et al.[5] Similarly, Mahadevan and co-workers have reported the microwave-assisted synthesis from 3-formyl-quinoline-2-thiones with active methylene esters.[6] All these methods have some limitations such as high temperature, longer reaction time and poor yields and to the best of our knowledge less explored on their 2-thione analogs.[7]

Our group is actively engaged in developing the easily accessible precursors of quinoline derivatives[8] for exploring their reactivity and synthetic applications. We have reported the synthesis of cyclopenta, pyrano- and pyrido-annulated quinolines using 2-chloro-3-formylquinoline precursor via intra and intermolecular cyclization of alkenes/alkynes by choice of suitable reagents, catalysts and other reactive partners.[9]

Further, we have also reported the rapid base-free one-pot synthesis of 1,2-dihydrobenzo[*b*][1,8]naphthyridines from Baylis Hillman acetates of 2-chloro-3-formylquinolines with different amines (approx. 5 min) with excellent yields.[10] This observation inspired us to explore the similar reactions for sulfur analogs using Na_2S to the synthesis of thiopyranoquinolines from Baylis Hillman reaction. The reaction with Na_2S proceeded to give a mixture of unidentified products. Subsequently, we turned our attention to multicomponent reaction using 2-chloro-3-formylquinolines, Na_2S, acrylonitrile, with different bases which again afforded the mixture of undesired products. We then focused on Michael addition followed by cyclization reactions on 2-thione analogs of 3-formylquinolines using acrylonitrile and bases. To our surprise, the reaction was domino and afforded the single desired product **3** in a very short time. Thus, we now report rapid and efficient one-pot synthesis of thiopyrano[2,3-*b*]quinolines from 3-formyl-quinoline-2-thiones with acrylonitrile and Et_3N base.

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0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.04.032

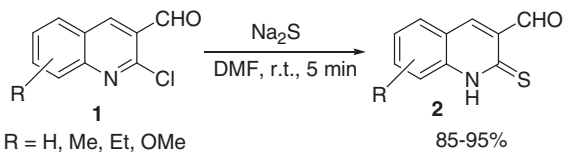
Initially, we attempted multicomponent reactions using substrate 2-chloro-3-formylquinoline (**1a**), Na_2S, acrylonitrile and base all together and also by sequential addition of the reagents with and without base at room temperature/heating, the reactions proceeded but failed to afford the desired cyclized product 2*H*-thiopyrano[2,3-*b*]quinoline-3-carbonitrile **(3a)**.

Next, we turn our attention to the Michael addition/cyclization reactions to the synthesis of **3**, using 3-formyl-quinoline-2-thione derivatives **2** as substrates, prepared from the compounds **1** using 1.5 equiv sodium sulfide in DMF at room temperature (85–95%, Scheme 1), for finding the optimization reaction conditions. Thus, 3-formyl-quinoline-2-thione (**2a**) was treated with 1.5 equiv acrylonitrile, 1.5 equiv Et_3N in 4.0 mL DMF at room temperature, the reaction was completed in 5 min and afforded only a single product with 93% yield, which was characterized from its spectral and analytical data as 2*H*-thiopyrano[2,3-*b*]quinoline-3-carbonitrile (**3a**) (Scheme 2, Table 1, entry 1).

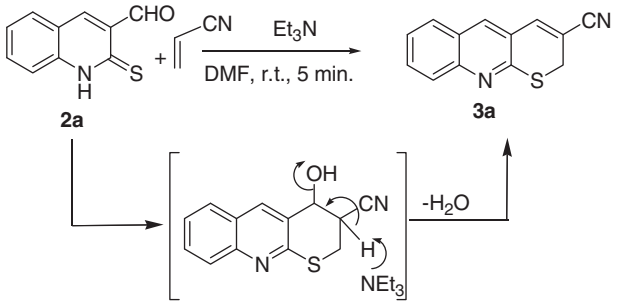
We further examined various parameters such as solvents and bases to optimize the reaction conditions for cyclization. The results are reported in Table 1 (entries 1–14). Among the bases, Et_3N afforded the pure cyclized product without further purification in excellent yield (entry 1). DBU base was found equally effective and afforded similar yield of the cyclized product (entry 2). However, using DABCO base, the cyclized product was found in lower yield (entry 3). It is noteworthy that, the reaction was also completed in 5 min using inorganic bases such as K_2CO_3,·Cs_2CO_3, *t*-BuOK and K_3PO_4 but afforded the mixture of unidentified products (Table 1, entries 4–7). Thus, it is found that organic bases are more efficient than the inorganic bases for the addition/cyclization reactions. We further examined the effect of various solvents such as DMF, $CHCl_3$, THF, CH_3CN, DCM, Toluene, MeOH and H_2O. The results are reported in Table 1 (entries 8–14). It was found that DMF solvent gave the best yield (93%, Table 1, entry 1) whereas $CHCl_3$ and THF were equally effective as DMF with slightly lower yields, respectively (88%, 80%, Table 1, entries 8 and 9). With CH_3CN and DCM the same product was obtained in 5 min with moderate yields (Table 1, entries 10 and 11). It is noteworthy that with nonpolar solvent like toluene and protic polar solvents such as MeOH and H_2O reaction did not proceed (entries 12–14).

With optimal conditions in hand, various substituted quinolines **2b–i** were allowed to react with acrylonitrile for the cyclizations. All reactions proceeded smoothly and provided the corresponding thiopyrano[2,3-*b*]quinolines **3b–i** in good to excellent yields. The results are summarized in Table 2 (entries 2–9). The similar reaction rates were observed with electron-donating and electron-withdrawing substituents on the quinoline moiety. However, the yields with electron donating substituents at positions 6 and 7 in **3b–c** and **3e–f** are slightly higher (entries 2, 3, 5 and 6) as compared to electronwithdrawing substituents at 6 and 7 positions in **3d** and **3g**, respectively (entries 4 and 7).

We further examined the reactions with other activated alkenes under similar reaction conditions such as ester (methylacrylate) and aldehyde (crotonaldehyde) to understand the effect of the substituents of the activated alkene on the reaction rate and yields. In both cases, reaction proceeded smoothly affording the desired cyclized product in 15 min with 88% and 71% yield, respectively (Table 2, entries 10 and 11), presuming the reaction rate was dependent on the substituents of the alkenes.



Scheme 1. Synthesis of precursor 3-formyl-quinoline-2-thiones.



Scheme 2. Synthesis of thiopyrano[2,3-*b*]quinoline (**3a**) from 3-formyl-quinoline-2-thione (**2a**).

Table 1
Optimization of reaction condition using different bases and solvents

Entry	Substrate	Base	Solvent	Product	Yield of **3a** (%)
1	**2a**	Et_3N	DMF	**3a**	93
2	**2a**	DBU	DMF	**3a**	90
3	**2a**	DABCO	DMF	**3a**	76
4	**2a**	K_2CO_3	DMF	**3a**	00
5	**2a**	Cs_2CO_3	DMF	**3a**	00
6	**2a**	*t*-BuOK	DMF	**3a**	00
7	**2a**	K_3PO_4	DMF	**3a**	00
8	**2a**	Et_3N	$CHCl_3$	**3a**	88
9	**2a**	Et_3N	THF	**3a**	80
10	**2a**	Et_3N	CH_3CN	**3a**	42
11	**2a**	Et_3N	DCM	**3a**	50
12	**2a**	Et_3N	Toluene	**3a**	00
13	**2a**	Et_3N	MeOH	**3a**	00
14	**2a**	Et_3N	H_2O	**3a**	00

Table 2
Synthesis of thiopyrano[2,3-*b*]quinolines **3** from 3-formyl-quinoline-2-thiones **2**

Entry	Substrate	R	Product	Time (min)	Yield of **3** (%)
1	**2a**	H	**3a**	5	93
2	**2b**	6-Me	**3b**	5	93
3	**2c**	6-OMe	**3c**	5	89
4	**2d**	6-Br	**3d**	5	85
5	**2e**	7-Me	**3e**	5	90
6	**2f**	7-OMe	**3f**	5	89
7	**2g**	7-Cl	**3g**	5	81
8	**2h**	8-Me	**3h**	5	86
9	**2i**	8-Et	**3i**	5	85
10[a]	**2a**	H	**3j**	15	88
11[b]	**2a**	H	**3k**	15	71

[a] Methyl acrylate.
[b] Crotonaldehyde used.

In conclusion, we have developed the conditions for domino reaction to the rapid and efficient synthesis of thiopyrano[2,3-*b*]quinolines using cheap base Et_3N. Experimental procedures[11] are simple and eliminate the need of anhydrous solvent, inert atmosphere and further purifications. The final compounds could be used as a valuable synthon in various organic transformations. Further, investigations of the compound with the various binucleophiles to the synthesis of annulated heterocycles are on underway.

Acknowledgments

We thank the CSIR (New Delhi) and the UGC (New Delhi) for funding. B.S. is thankful to the CSIR, New Delhi, for the award of Senior Research Fellowship, A.C. to the UGC, New Delhi for DSK-Postdoctoral fellowship and M.A. to the BHU fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.04.032. These data include MOL files and InChiKeys of the most important compounds described in this article.

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11. To a stirred solution of **2** (0.25 mmol) in DMF (4 mL) was added acrylonitrile (0.37 mmol) and Et3 N (0.37 mmol) at room temperature for 5–15 min. After completion of the reaction (as monitored by TLC), the reaction mixture was allowed to pour into chilled water and precipitate was filtered out. The crude product **3** was pure enough for analysis; 2*H*-thiopyrano[2,3-*b*]quinoline-3-carbonitrile (**3a**): light yellow solid; yield: 93%; mp 153 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.93 (s, 2H), 7.49 (t, J = 7.2 Hz, 1H), 7.69–7.75 (m, 3H), 7.82 (s, 1H), 7.91 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.7, 106.5, 117.7, 123.7, 126.9, 128.2, 128.3, 129.2, 131.8, 136.6, 140.9, 148.4, 155.7; IR (KBr): 1579, 2204 cm^{-1}. HRMS calcd for $C_{13}H_9N_2S$ $[M+H]^+$ 225.0486; found 225.0483.