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Tetrahedron Letters 47 (2006) 4381–4383
Tetrahedron Letters

Lanthanum(III) nitrate hexahydrate or *p*-toluenesulfonic acid catalyzed one-pot synthesis of 4(3*H*)-quinazolinones under solvent-free conditions☆,☆☆

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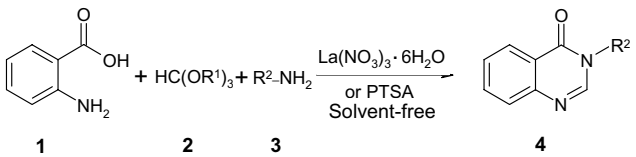
Received 17 March 2006; revised 12 April 2006; accepted 20 April 2006
Available online 12 May 2006

Abstract—The one-pot synthesis of quinazolinone derivatives from the reaction of anthranilic acid, trialkyl orthoformate and amines in the presence of lanthanum(III) nitrate hexahydrate or *p*-toluenesulfonic acid has been carried out. The reaction occurred in a few minutes under solvent-free conditions and in excellent yields.

4(3*H*)-Quinazolinones are an important class of fused heterocycles with a wide range of biological activities such as anti-cancer, anti-inflammatory, anti-convulsant, anti-hypertensive and anti-malarial activity.[1] Several bio-active natural products including febrifugine and isofebrifugine contain a quinazolinone moiety and possess anti-malarial activity.[2,3] The most common methods for the preparation of quinazolinones involve the amidation of 2-aminobenzonitrile or 2-aminobenzoic acid or its derivatives followed by oxidative ring closure under basic conditions.[4,5] Other methods involve cycloaddition of anthranilic acid derivatives with a diverse range of substrates including imidates and iminohalides.[6] Recently, 4(3*H*)-quinazolinones were prepared using silica sulfuric acid,[7] PCl_3[8] and $Zn/HCOONH_4$ under microwave irradiation.[9] However, some of these methods are associated with drawbacks such as multistep procedures, costly reagents, harsh reaction conditions, complex and tedious experimental procedures, and low yields. Thus, several previous methods have been excluded from practical applications due to environmental and economic considerations. Hence, there is still a need to develop efficient methods for the synthesis of 4(3*H*)-quinazolinones.

We have developed an expeditious one-pot synthesis of 4(3*H*)-quinazolinones from the reaction of anthranilic acid, trialkyl orthoformate and amines (alkyl or aryl) in the presence of lanthanum(III) nitrate hexahydrate [$La(NO_3)_3{\cdot}6H_2O$] or *p*-toluenesulfonic acid (PTSA) under solvent-free conditions (Scheme 1).

Various 4(3*H*)-quinazolinones were prepared[10] (Table 1) by reacting anthranilic acid **1** with different substituted alkyl and aryl amines and trimethyl or triethyl orthoformate. The reaction proceeded at room temperature within few minutes in excellent yields after the addition of the acid catalyst lanthanum(III) nitrate hexahydrate or *p*-toluenesulfonic acid. Only the reaction with 4-nitroaniline required reflux and the time required was 15 min.



Scheme 1.

Keywords: Quinazolinones; Lanthanum(III) nitrate hexahydrate; *p*-Toluenesulfonic acid; Three-component reaction; Solvent-free conditions.

☆ Reactions using lanthanum(III) nitrate hexahydrate, paper 3; for paper 2 refer to Ref. 12.

☆☆ IICT Communication No. 060415.

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0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.04.096

Table 1. Preparation of 4(3*H*)-quinazolinones using $La(NO_3)_3{\cdot}6H_2O$ and PTSA under solvent-free conditions[a]

Entry	R^1	R^2	Catalyst[b]	Time (min)	Isolated yield (%)
a	Me	C_6H_5	i	5	98[6h]
			ii	5	96
b	Me	2-MeC_6H_4	i	5	97[6h]
			ii	5	93
c	Me	4-MeC_6H_4	i	5	98[6h]
			ii	5	96
d	Me	2-FC_6H_4	i	5	94
			ii	5	92
e	Me	4-FC_6H_4	i	5	96[6h]
			ii	5	92
f	Me	2-$MeOC_6H_4$	i	5	95[6h]
			ii	5	93
g	Me	4-$NO_2C_6H_4$	i	15	84[6h]
			ii	15	81
h	Me	1-Naphthyl	i	10	92
			ii	10	86
i	Me	$C_6H_5CH_2CH_2$	i	5	94
			ii	5	94
j	Me	$C_6H_5CHCH_3$	i	5	92
			ii	5	91
k	Me	$C_6H_5CH(CH_2)_2CH_3$	i	10	95
			ii	10	92
l	Et	C_6H_5	i	5	97[6h]
			ii	5	96
m	Et	2-MeC_6H_4	i	5	98[6h]
			ii	5	91
n	Et	4-MeC_6H_4	i	5	96[6h]
			ii	5	96
o	Et	2-FC_6H_4	i	5	93
			ii	5	90
p	Et	4-FC_6H_4	i	5	90[6h]
			ii	5	90
q	Et	2-$MeOC_6H_4$	i	5	96[6h]
			ii	5	93
r	Et	4-$NO_2C_6H_4$	i	15	85[6h]
			ii	15	82
s	Et	1-Naphthyl	i	10	92
			ii	10	92
t	Et	$C_6H_5CH_2CH_2$	i	5	96
			ii	5	93
u	Et	$C_6H_5CHCH_3$	i	10	91
			ii	10	91
v	Et	$C_6H_5CH(CH_2)_2CH_3$	i	15	96
			ii	15	90

[a] The structures of the quinazolinone derivatives were determined from their spectral (^1H NMR and MS) and analytical data.
[b] Catalyst i: $La(NO_3)_3{\cdot}6H_2O$, ii: PTSA.

This is due to the presence of an electron withdrawing group (–NO_2). Triethyl and trimethyl orthoformates reacted similarly. Both $La(NO_3)_3{\cdot}6H_2O$ and PTSA catalyze the reaction under homogeneous conditions. $La(NO_3)_3{\cdot}6H_2O$ was recently used as a catalyst for the deprotection of acetonides[11] and in selective protection of primary alcohols.[12] PTSA is widely used in organic synthesis.[13]

In conclusion, we have developed a simple and efficient three-component reaction of anthranilic acid, orthoesters and alkyl/aryl amines using $La(NO_3)_3{\cdot}6H_2O$ or PTSA under the solvent-free conditions for the preparation of 4(3*H*)-quinazolinones in a single step. The mildness of the catalysts, solvent-free conditions, fast reaction times (5–15 min), simple experimental procedure and excellent yields (82–98%) are the great advantages of the present protocol.

Acknowledgements

The authors thank CSIR, New Delhi, India for financial assistance and Dr. J. S. Yadav, Director, IICT, for his constant encouragement.

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10. General procedure for the preparation of quinazolinones: To a mixture of anthranilic acid (1 mmol), an ortho ester (1.2 mmol) and an amine (1.2 mmol) $La(NO_3)_3{\cdot}6H_2O$ (5 mmol%) or PTSA (5 mmol %) were added. The mixture was stirred at room temperature for the appropriate time (Table 1). After completion of the reaction, as monitored by TLC, water was added followed by extraction into dichloromethane (3 × 5 mL). The combined organic layer was washed with aq HCl (5%) (3 × 5 mL) and washed with saturated $NaHCO_3$ (3 × 5 mL) solution. The organic layer

was dried over $MgSO_4$ and the solvent was evaporated to afford pure 4(3*H*)-quinazolinones.

The spectral (^{1}H NMR and MS) and analytical data of some representative 4(3*H*)-quinazolinones are given below.

Compound **4d**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.22 (d, 1H, $J = 7.3$ Hz), 7.15 (m, 4H), 7.03 (m, 4H); EIMS: *m*/*z* 240 ($M^{+\cdot}$); Anal. Calcd for $C_{14}H_9N_2FO$: C, 69.99; H, 3.77; F, 7.90; N, 11.66. Found: C, 69.82; H, 3.61; N, 11.59. Compound **4h**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.72 (m, 7H), 7.08 (m, 4H); EIMS: *m*/*z* 272 ($M^{+\cdot}$); Anal. Calcd for $C_{18}H_{12}N_2O$: C, 79.39; H, 4.44; N, 10.28. Found: C, 79.22; H, 4.54; N, 10.31. Compound **4i**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.32 (d, 1H, $J = 7.7$ Hz), 7.62 (m, 4H), 7.20 (m, 5H), 4.22 (t, 2H, $J = 2.5$ Hz), 3.28 (t, 2H, $J = 2.5$ Hz); EIMS: *m*/*z* 250 ($M^{+\cdot}$). Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.77; H, 5.63; N, 11.19. Found: C, 76.82; H, 5.76; N, 11.24. Compound **4j**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.28 (d, 1H, $J = 7.5$ Hz), 7.58 (m, 4H), 7.22 (m, 5H), 6.38 (m, 1H), 1.80 (d, 3H, $J = 3.5$ Hz); EIMS: *m*/*z* 250 ($M^{+\cdot}$). Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.77; H, 5.63; N, 11.19. Found: C, 76.72; H, 5.59; N, 11.28. Compound **4k**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.30 (d, 1H, $J = 7.2$ Hz), 7.32 (m, 4H), 7.16 (m, 5H), 6.37 (t, 1H, $J = 2.5$ Hz), 1.72 (m, 2H), 1.32 (m, 2H), 0.91 (t, 3H, $J = 1.05$ Hz); EIMS: *m*/*z* 278 ($M^{+\cdot}$). Anal. Calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.51; N, 10.06. Found: C, 77.59; H, 6.62; N, 10.14.

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