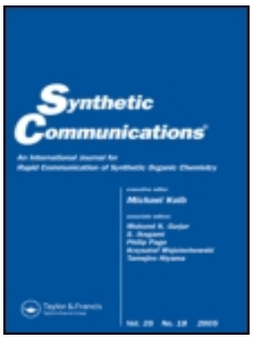

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Synthesis of 4-Hydroxy-3-(1-aryl-2-acetylethyl)-7,8-diaryl-2H-thieno(3,2-h)chromen-2-ones Using Cerium(III) Chloride

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Abstract: A new series of 4-hydroxy-3-(1-aryl-2-acetylethyl)-7,8-diaryl-2H-thieno(3,2-h)chromen-2-ones were synthesized in good yields by reacting 4-hydroxy-7,8-diaryl-2H-thieno(3,2-h)chromen-2-ones with various α,β-unsaturated ketones in presence of cerium(III) chloride in acetonitrile.

Keywords: Cerium(III) chloride hepta hydrate; electron-deficient olefins; 4-hydroxy-7,8-diaryl-2H-thieno(3,2-h)chromen-2-ones; Michael condensation

INTRODUCTION

A large number of natural products contain the coumarin heterocyclic nucleus, which has in biological and medicinal applications.[1,2] Coumarin and its derivatives are widely used as additives in food, perfumes, cosmetics, pharmaceuticals, and agrochemicals.[3,4] Particularly, 3-substituted-4-hydroxy coumarin and its derivatives have powerful anticoagulant activity in vivo in many of animal species. The structure–activity relationship of these compounds in rabbits has been thoroughly studied.[5] 3-(2-Acetyl phenyl ethyl)-4-hydroxy coumarin (warfarin) is the best-known oral anticoagulant rodenticide.[6] Warfarins were obtained in very low yield by Michael condensation of 4-hydroxy coumarins with benzal acetones (arylideneacetones) in the presence of piperidine.[7] So, the preparation of new warfarin analogs are established using cerium(III)

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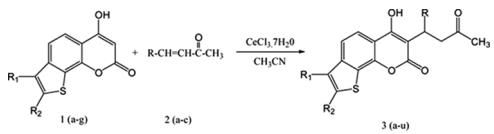
chloride as catalyst in acetonitrile. This article the synthesis of 4-hydroxy-3-(1-aryl-2-acetylethyl)-7,8-diaryl-2H-thieno(3,2-h)chromen-2-ones (**3a–u**) by condensation of 4-hydroxy-7,8-diaryl-2H-thieno(3,2-h)chromen-2-ones (**1a–g**) with various α, β-unsaturated ketones in the presence of cerium(III) chloride in acetonitrile. We have observed that when cerium(III) chloride heptahydrate was used instead of piperidine in Michael condensation, warfarin derivatives (**3a–u**) were obtained in good yields and reaction times and temperature were also reduced. Cerium(III) chloride heptahydrate had been used in organic synthesis as a substitute for a Lewis acid in preparation of heterocyclic compounds and other condensation products.[8] It is an important catalyst for condensation reactions and it is also a commercially available lanthanide reagent, nontoxic, and easy to handle without further purification.[9]

RESULTS AND DISCUSSION

In continuation of our work on the synthesis of novel fused heterocyclic systems,[10] this article reveals an efficient synthesis of 4-hydroxy-3-(1-aryl-2-acetylethyl)-7,8-diaryl-2H-thieno(3,2-h)chromen-2-ones (**3a–u**) using $CeCl_3 \cdot 7H_20$ as catalyst. Various α,β-unsaturated ketones (**2a–c**) were condensed with 4-hydroxy-7,8-diaryl-2H-thieno(3,2-h)chromen-2-ones (**1a–g**) at room temperature in acetonitrile in the presence of 10% mol $CeCl_3 \cdot 7H_2O$ to give 4-hydroxy-3-(1-aryl-2-acetylethyl)-7,8-diaryl-2H-thieno(3,2-h)chromen-2-ones (**3a–u**) with more than 70% yields (Scheme 1), (Table 1). These warfarins (**3a–u**) were also prepared by condensation of 4-hydroxy-7,8-diaryl-2H-thieno(3,2-h)chromen-2-ones (**1a–g**) with electron-deficient arylidene acetones (**2a–c**) in piperidene and dioxane. The yields were obtained in less than 50%, and 8–9 h is required to complete the reaction at 70–80°C. Cerium(III) chloride heptahydrate with acetonitrile is highly suitable for the Michael condensation at room temperature. It is interesting to note that by employing cerium(III) chloride heptahydrate for this reaction in acetonitrile medium, the reaction time also decreased to 2–3 from 8–9 h.

All the compounds (**3a–u**) are confirmed by IR, ^{1}H NMR, and mass spectra. In IR, the absorption bands are observed around 3400–3500 cm^{-1}, due to enolic form of the coumarin. The lactone



Scheme 1. Synthesis of 4-hydroxy-3-(1-aryl-2-acetylethyl)-7,8-diaryl-2H-thieno.

Table 1. Synthesis of substituted 4-hydroxy-3-(1-aryl-2-acetylethyl)-7,8-diaryl-2H-thieno

Compound	R	R_1	R_2	Time (h)	Temp (°C)	Yield
3a	$-C_6H_5$	$-C_6H_5-$	$-C_6H_5$	2	25–30	78
3b	$-C_6H_3Cl_2$-(3,4)	$-C_6H_5-$	$-C_6H_5$	2	25–30	73
3c	$-C_6H_5OH$-(p)	$-C_6H_5$	$-C_6H_5$	2	25–30	71
3d	$-C_6H_5$	$-C_6H_4Br$(p)	$-C_6H_5$	2	25–30	74
3e	$-C_6H_3Cl_2$-(3,4)	$-C_6H_4Br$(p)	$-C_6H_5$	2	25–30	73
3f	$-C_6H_5OH$-(p)	$-C_6H_4Br$(p)	$-C_6H_5$	2	25–30	71
3g	$-C_6H_5$	$-C_6H_4CH_3$-(p)	$-C_6H_5$	3	25–30	75
3h	$-C_6H_3Cl_2$-(3,4)	$-C_6H_4CH_3$-(p)	$-C_6H_5$	3	25–30	74
3i	$-C_6H_5OH$-(p)	$-C_6H_4CH_3$-(p)	$-C_6H_5$	3	25–30	70
3j	$-C_6H_5$	$-C_6H_3Cl_2$(3,4)	$-C_6H_5$	3	25–30	70
3k	$-C_6H_3Cl_2$-(3,4)	$-C_6H_3Cl_2$(3,4)	$-C_6H_5$	3	25–30	72
3l	$-C_6H_5OH$-(p)	$-C_6H_3Cl_2$(3,4)	$-C_6H_5$	3	25–30	72
3m	$-C_6H_5$	$-C_6H_3Cl_2$(3,4)	$-C_6H_4Br$-(p)	3	25–30	73
3n	$-C_6H_3Cl_2$-(3,4)	$-C_6H_3Cl_2$(3,4)	$-C_6H_4Br$-(p)	3	25–30	78
3o	$-C_6H_5OH$-(p)	$-C_6H_3Cl_2$(3,4)	$-C_6H_4Br$-(p)	3	25–30	77
3p	$-C_6H_5$	$-C_6H_3Cl_2$(3,4)	$-C_6H_4CH_3$-(p)	3	25–30	71
3q	$-C_6H_3Cl_2$-(3,4)	$-C_6H_3Cl_2$(3,4)	$-C_6H_4CH_3$-(p)	3	25–30	70
3r	$-C_6H_5OH$-(p)	$-C_6H_3Cl_2$(3,4)	$-C_6H_4CH_3$-(p)	3	25–30	76
3s	$-C_6H_5$	$-C_6H_5$	$-C_6H_3F_2$(3,4)	3	25–30	77
3t	$-C_6H_3Cl_2$-(3,4)	$-C_6H_5$	$-C_6H_3F_2$(3,4)	3	25–30	70
3u	$-C_6H_5OH$-(p)	$-C_6H_5$	$-C_6H_3F_2$(3,4)	3	25–30	73

coumarin carbonyl stretching is observed around 1715–1720 cm^{-1} and the ketone carbonyl of the side chain is present at 1680 cm^{-1}. The IR band at 750 cm^{-1} is due to the vibration of thiophene ring. The ^1H NMR spectra contains the characteristic signals both for the starting materials and for the final products. The starting substituted 4-hydroxycoumarins (**1a–g**) exhibit a signal around 6.2–6.4 δ for the 3-H of the 4-hydroxy coumarin. This signal disappears in the final products (**3a–u**), indicating the formation of the Michael product. The ^1H NMR spectra also contain the peaks for CH_3-CO around 2.3 to 2.5 δ and -CH2- at a little higher field around 3 δ. All the mass spectra indicate a fragmentation pattern uniformly losing CH_3CO of the side chain followed by the loss of the lactone carbonyl.

EXPERIMENTAL

All materials were obtained from commercial suppliers and used without further purification. Standard distilled water was used throughout the

study. All reactions were carried out in air. NMR spectra were recorded at 293 K on a 400-MHz instrument using $CDCl_3$ and d_6-DMSO as solvent and TMS as internal reference. IR spectra were recorded as KBr pellets using a Shimadzu 8010 FTIR spectrophotometer. Mass spectra were recorded on a VG Micromass 7070H (F or CI) auto spectrometer. Products were purified by column chromatography (Aldrich) using 100- to 200-mesh silica gel.

Synthesis of 4-Hydroxy-3-(1-aryl-2-acetyl-ethyl)-7,8-diaryl-2H-thieno(3,2-h)chromen-2-ones

4-Hydroxy-7,8-diphenyl-2h-thieno(3,2-h)chromen-2-ones (3 mmol) were added to a solution of benzylidene (3 mmol) and $CeCl_3 \cdot 7H_2O$ (10%) in acetonitrile (6 ml) and stirred at 25–30°C for 2–3 h. The reaction had been monitored by thin-layer chromatography (TLC) (hexane–ethyl acetate 5: 1). After completion of the reaction, demineralized (DM) water (6 ml) was added to the reaction mixture at 25–30°C and extracted with ethyl acetate (2×20 ml). The combined organic layers were washed with 10% (w/v) brine solution and then dried over Na_2SO_4, concentrated in vacuum, and purified by column chromatography on silica gel to afford the pure product.

Data

4-Hydroxy-3-(1-phenyl-2-acetyl-ethyl)-7,8-diphenyl-2H-thieno(3,2-h) chromen-2-one **(3a)**

IR (KBr, cm^{-1}): 1715, 1682, 756. ^1H NMR (300 MHz, $CDCl_3$): δ: 2.38 (3H, s, CH_3), 2.98–3.10 (2H, m, -CH_2), 4.40–4.52 (1H, dd, -CH), 7.10–8.39 (17H, m, Ar-H); MS: m/z 516 (M^+).

4-Hydroxy-3-(1-o,p-dichlorophenyl-2-acetyl-ethyl)-7,8-diphenyl-2H-thieno(3,2-h)chromen-2-one **(3b)**

IR (KBr, cm^{-1}): 750, 1680, 1720 and 3446 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ: 2.41 (3H, s, CH_3), 2.98–3.18 (2H, m, -CH_2), 4.38–4.46 (1H, dd, -CH), 6.96–8.16 (15H, m, Ar-H); MS: m/z 584 (M^+).

4-Hydroxy-3-(1-p-hydroxyphenyl-2-acetyl-ethyl)-7,8-diphenyl-2H-thieno(3,2-h)chromen-2-one **(3c)**

IR (KBr, cm^{-1}): 750, 1680, 1720 and 3500 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ: 2.40 (3H, s, CH_3), 3.00–3.28 (2H, m, -CH_2), 4.32–4.39

(1H, dd, -CH), 7.06–8.28 (16H, m, Ar-H), 10.36 (1H, s, -OH), 11.86 (1H, s, -OH); MS: m/z 532 (M^+).

4-Hydroxy-3-(1-p-hydroxyphenyl-2-acetyl-ethyl)-7-(p-bromophenyl)-8-phenyl-2H-thieno(3,2-h)chromen-2-one **(3d)**

IR (KBr, cm^{-1}): 755, 1680, 1715 and 3460 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ: 2.36 (3H, s, CH_3), 3.04–3.26 (2H, m, $-CH_2$), 4.35–4.43 (1H, dd, -CH), 7.02–8.30 (16H, m, Ar-H); MS: m/z 595 (M^+).

4-Hydroxy-3-(1-o,p-dichlorophenyl-2-acetyl-ethyl)-7-p-bromophenyl-8-phenyl-2H-thieno(3,2-h)chromen-2-one **(3e)**

IR (KBr, cm^{-1}): 752, 1680, 1715 and 3440 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ: 2.40 (3H, s, CH_3), 2.80–3.15 (2H, m, $-CH_2$), 4.40–4.48 (1H, dd, -CH), 7.03–8.315 (14H, m, Ar-H); MS: m/z 663 (M^+).

4-Hydroxy-3-(1-p-hydroxyphenyl-2-acetyl-ethyl)-7-p-bromophenyl-8-phenyl-2H-thieno(3,2-h)chromen-2-one **(3f)**

IR (KBr, cm^{-1}): 755, 1686, 1710 and 3480 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ: 2.42 (3H, s, CH_3), 3.00–3.28 (2H, m, $-CH_2$), 4.43–4.52(1H, dd, -CH), 7.04–8.28 (15H, m, Ar-H); MS: m/z 611 (M^+).

4-Hydroxy-3-(1-phenyl-2-acetyl-ethyl)-7-p-tolyl-8-phenyl-2H-thieno(3,2-h)chromen-2-one **(3 g)**

IR (KBr, cm^{-1}): 756, 1682, 1720 and 3455 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ: 1.88 (3H, s, CH_3), 2.33 (3H, s, CH_3), 2.86–3.20 (2H, m, $-CH_2$), 4.36–4.45 (1H, dd, -CH), 7.00–8.34 (16H, m, Ar-H); MS: m/z 530 (M^+).

4-Hydroxy-3-(1-o,p-dichlorophenyl-2-acetyl-ethyl)-7-p-tolyl-8-phenyl-2H-thieno(3,2-h)chromen-2-one **(3 h)**

IR (KBr, cm^{-1}): 755, 1680, 1710 and 3440 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ: 1.72 (3H, s, CH_3), 2.40 (3H, s, CH_3), 2.98–3.10 (2H, m, $-CH_2$), 4.42–4.53 (1H, dd, -CH), 7.10–8.25 (14H, m, Ar-H); MS: m/z 598 (M^+).

4-Hydroxy-3-(1-p-hydroxyphenyl-2-acetyl-ethyl)-7-p-tolyl-8-phenyl-2H-thieno(3,2-h)chromen-2-one **(3i)**

IR (KBr, cm^{-1}): 755, 1680, 1715 and 3452 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ: 1.82 (3H, s, CH_3), 2.36 (3H, s, CH_3), 3.04–3.22 (2H, m, -CH_2), 4.45– 4.58 (1H, dd, -CH), 7.05–8.28 (15H, m, Ar-H); MS: m/z 546 (M^+).

4-Hydroxy-3-(1-phenyl-2-acetyl-ethyl)-7-o,p-dichlorophenyl-8-phenyl-2H-thieno(3,2-h)chromen-2-one **(3j)**

IR (KBr, cm^{-1}): 750, 1680, 1710 and 3486 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ: 2.35 (3H, s, CH_3), 2.98–3.12 (2H, m, -CH_2), 4.35–4.43 (1H, dd, -CH), 7.15–8.35 (15H, m, Ar-H); MS: m/z 584 (M^+).

4-Hydroxy-3-(1-o,p-dichlorophenyl-2-acetyl-ethyl)-7-o, p-dichlorophenyl-8-phenyl-2H-thieno(3,2-h)chromen-2-one **(3k)**

IR (KBr, cm^{-1}): 750, 1680, 1710 and 3450 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ: 2.40 (3H, s, CH_3), 3.06–3.36 (2H, m, -CH_2), 4.38–4.46 (1H, dd, -CH), 7.16–8.25 (13H, m, Ar-H); MS: m/z 652 (M^+).

4-Hydroxy-3-(1-p-hydroxyphenyl-2-acetyl-ethyl)-7-o, p-dichlorophenyl-8-phenyl-2H-thieno(3,2-h)chromen-2-one **(3l)**

IR (KBr, cm^{-1}): 750, 1680, 1715 and 3460 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ: 2.40 (3H, s, CH_3), 3.02–3.32 (2H, m, -CH_2), 4.43–4.50 (1H, dd, -CH), 6.96–8.15 (12H, m, Ar-H); MS: m/z 600 (M^+).

4-Hydroxy-3-(1-phenyl-2-acetyl-ethyl)-7-o,p-dichlorophenyl-8-phenyl-2H-thieno(3,2-h)chromen-2-one **(3m)**

IR (KBr, cm^{-1}): 756, 1680, 1710 and 3480 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ: 2.42 (3H, s, CH_3), 3.00–3.38 (2H, m, -CH_2), 4.40–4.53 (1H, dd, -CH), 6.98–8.20 (14H, m, Ar-H); MS: m/z 663 (M^+).

4-Hydroxy-3-(1-o,p-dichlorophenyl-2-acetylethyl)-7-o, p-dichlorophenyl-8-p-bomophenyl-2H-thieno(3,2-h)chromen-2-one **(3n)**

IR (KBr, cm^{-1}): 755, 1675, 1710 and 3450 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ: 2.40 (3H, s, CH_3), 2.98–3.32 (2H, m, -CH_2), 4.36–4.48 (1H, dd, -CH), 7.02–8.22 (12H, m, Ar-H); MS: m/z 731 (M^+).

4-Hydroxy-3-(1-p-hydroxyphenyl-2-acetyl-ethyl)-7-o,p-dichlorophenyl-8-p-bomophenyl-2H-thieno(3,2-h)chromen-2-one **(3o)**

IR (KBr, cm^{-1}): 750, 1680, 1710 and 3468 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ: 2.38 (3H, s, CH_3), 3.07–3.40 (2H, m, -CH_2), 4.40–4.52 (1H, dd, -CH), 7.12–8.26 (12H, m, Ar-H); MS: m/z 679 (M^+).

4-Hydroxy-3-(1-phenyl-2-acetyl-ethyl)-7-o,p-dichlorophenyl-8-tosyl-2H-thieno(3,2-h)chromen-2-one **(3p)**

IR (KBr, cm^{-1}): 750, 1675, 1720 and 3450 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ: 2.40 (3H, s, CH_3), 2.97–3.34 (2H, m, -CH_2), 4.30– 4.40 (1H, dd, -CH), 7.05–8.26 (14H, m, Ar-H); MS: m/z 598 (M^+).

4-Hydroxy-3-(1-o,p-dichlorophenyl-2-acetyl-ethyl)-7-o,p-dichlorophenyl-8-tosyl-2H-thieno(3,2-h)chromen-2-one **(3q)**

IR (KBr, cm^{-1}): 755, 1680, 1710 and 3436 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ: 2.36 (3H, s, CH_3), 3.04–3.38 (2H, m, -CH_2), 4.35–4.44 (1H, dd, -CH), 7.12–8.18 (12H, m, Ar-H); MS m/z 666 (M^+).

4-Hydroxy-3-(1-p-hydroxyphenyl-2-acetyl-ethyl)-7-o,p-dichlorophenyl-8-tosyl-2H-thieno(3,2-h)chromen-2-one **(3r)**

IR (KBr, cm^{-1}): 755, 1680, 1710 and 3490 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ: 2.42 (3H, s, CH_3), 3.02–3.38 (2H, m, -CH_2), 4.41–4.50 (1H, dd, -CH), 7.08–8.15 (13H, m, Ar-H); MS: m/z 614 (M^+).

4-Hydroxy-3-(1-phenyl -2-acetyl-ethyl)-7-phenyl-8-o,p-difluorophenyl-2H-thieno(3,2-h)chromen-2-one **(3s)**

IR (KBr, cm^{-1}): 750, 1676, 1715 and 3450 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ: 2.40 (3H, s, CH_3), 3.00–3.39 (2H, m, -CH_2), 4.38–4.49 (1H, dd, -CH), 7.04–8.23 (13H, m, Ar-H); MS: m/z 552 (M^+).

4-Hydroxy-3-(1-o,p-dichlorophenyl-2-acetylethyl)-7-phenyl-8-o,p-difluorophenyl-2H-thieno(3,2-h)chromen-2-one **(3t)**

IR (KBr, cm^{-1}): 750, 1680, 1710 and 3480 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ: 2.40 (3H, s, CH_3), 3.02–3.40 (2H, m, -CH_2), 4.33–4.42 (1H, dd, -CH), 7.02–8.16 (12H, m, Ar-H); MS: m/z 620 (M^+).

4-Hydroxy-3-(1-p-hydroxyphenyl-2-acetyl-ethyl)-7-phenyl-8-o,p-difluorophenyl-2H-thieno(3,2-h)chromen-2-one **(3u)**

IR (KBr, cm^{-1}): 755, 1680, 1720 and 3498 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ: 2.42 (3H, s, CH_3), 3.00–3.36 (2H, m, $-CH_2$), 4.38–4.51 (1H, dd, -CH), 7.06–8.12 (13H, m, Ar-H); MS: m/z 568 (M^+).

CONCLUSIONS

When cerium(III) chloride heptahydrate was used instead of piperidine in the Michael condensation, warfarin derivatives (**3a–u**) were obtained in good yields, and reaction times and temperature were also reduced.

ACKNOWLEDGMENT

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