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Facile synthetic route to benzo[*c*]chromenones and thieno[2,3-*c*]chromenones

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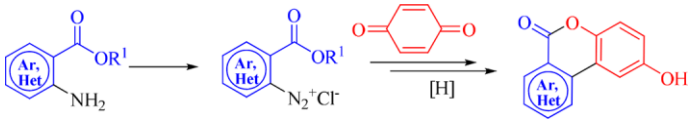
^{1}H and ^{13}C NMR spectra of all new compounds can be found via the ‘‘Supplementary Content’’ section of this article’s webpage.

ABSTRACT

Convenient two-step procedure for the synthesis of fused chromenone derivatives was developed. Reduction of the obtained in the Meerwein arylation reaction aryl- and thienylquinones allowed to construct 6*H*-benzo[*c*]chromene-6-ones and 4*H*-thieno[2,3-*c*]chromen-4-one in a cost and time- more effective manner in comparison with already known methods. The obtained products have provided a new entry to chromenone derivatives.

GRAPHICAL ABSTRACT



KEYWORDS: 4*H*-thieno[2,3-*c*]chromen-4-one, 6*H*-benzo[*c*]chromene-6-ones, diazonium salts, meerwein arylation reaction, quinone

Introduction

Recently, special attention is paid to the research in medicine, particularly to the synthetic drug development for the numerous diseases treatment. Strong interest of researchers in functionalized 6*H*-benzo[*c*]chromenone derivatives is determined by the broad spectrum of their biological activity and occurrence in pharmacologically relevant natural compounds [1 and articles cited therein]. Moreover, substituted 6*H*-benzo[c]chromenones are of considerable pharmacological importance due to the presence of chromenone core in a number of anticancer agents and antibiotics [2 and articles cited therein]. Taking into account the above stated, development of methods for the synthesis of new hydroxy-chromenone derivatives is encouraged and was in our focus.

However, synthesis of diverse heterocyclic molecules from the readily available starting materials in a cost and time-effective manner is an enduring challenge for organic chemists. The typical key approaches in the synthesis of 2-hydroxy-6*H*-benzo[*c*]chromene-6-ones or 8-hydroxy-4*H*-thieno[2,3-*c*]chromen-4-ones are as follows: a) Suzuki coupling of boronates/boronic acids with the corresponding aryl-/hetaryl- bromides [3–5]; b) Packmann condensation between 1,5-dihydronaphtalene and corresponding β-ketoesters to generate desired carbon framework with further two-step functionalization [6]; c) domino retro-Michael-aldol lactonization [7]; d) Hauser-initiated annulation [8,9]; e) catalytic intramolecular oxidation reaction of quinone with benzoic acids [10]; f) Rh(III)-, Ru(II) - and Copper- catalysed C−H bond arylation with phenol, quinone or arene derivatives.[11–14] The last approaches [13,14] present convenient and facile chromenone synthesis using modified Meerwein arylation method as a key step. Despite the vast amount of literature on synthetic routes to hydroxy chromenone derivatives, all mentioned above methods require the use of expensive or not readily available starting reactants, metal catalysts (Pd, Rh, Ir compounds), longer reaction times, high temperatures and sometimes give poor or moderate yields in multi-step procedures.

Due to the importance of fused chromenone derivatives the development of new efficient synthetic paths for their preparation still remains an actual task. Thus, considering the above synthetic methodology to prepare chromenones and its biological importance it was thought worthwhile to elaborate convenient synthetic protocol allowing to construct hydroxy chromenone derivatives under mild Meerwein arylation conditions from the readily available starting material.

Results and Discussion

Arylation of unsaturated compounds with arenediazonium salts under typical Meerwein conditions provides a convenient method for the synthesis of polyfunctional substrates. In our previous works, we demonstrated the synthetic potential of aryldiazonium salts in the construction of valuable heterocyclic compounds via the Meerwein arylation reactions with further cyclization.[15,16] Moreover, a wide variety of novel fused polyheterocyclic systems were successfully obtained in cyclocondensation reactions of thienyldiazonium salts.[17–19] Thus, we have used Meerwein arylation approach to obtain a number of substituted 2-hydroxy-6*H*-benzo[*c*]chromen-6-ones and 8-hydroxy-4*H*-thieno[2,3-*c*]chromen-4-one. Benzo[*c*]chromen-6-ones and thieno[2,3-*c*]chromenone were obtained via metal-free protocol in a cost and time-more effective manner in comparison with already known methods.

Firstly, it was found out that readily available substituted anthranilates **1** could be easily converted into corresponding diazonium salts **2**, which in the Meerwein arylation reaction with quinone give arylquinones **3**in high yields under mild conditions (Scheme 1). The reaction of arenediazonium chlorides **2a–d** with quinone were carried out in aqueous suspension in the presence of sodium acetate. The peculiarity of the 1,4-benzoquinone arylation is that it occurs in the absence of a catalyst, which is nearly always required in all other variants of the Meierwein reaction.

Next the reduction of obtained arylquinones **3** was performed resulting into 2',5'-dihydroxy-[1,1'-biphenyl]-2-carboxylate intermediate **A** formation. Obviously, the last intermediate **A** undergoes cyclization by intermolecular transesterification and the chromenone ring closure products **4** were isolated in high yields. It should be mentioned, that both reduction systems: sodium sulfide in aqueous ethanol (Method **A**) or zinc powder in glacial acetic acid (Method **B**) gave successful result yielding a number of desired benzo[*c*]chromen-6-ones **4**.

Additionally, we were interested to develop synthetic paths for 4*H*-thieno[2,3-*c*] chromen-4-one formation. Further to extend the application of proposed Meerwein methodology, we examined thienyldiazonium salts. Thus, new reaction partner: thienyldiazonium salt **2e** was involved in Meerwein arylation of quinone. Obtained in Meerwein thienylquinone **3e** was reduced in the same, mentioned earlier, protocol using sodium sulphide in aqueous ethanol affording desired fused thienochromenone **4e** formation in high yield.

It should be noted, that usage of diazonium salts based on 2-aminothiophenes in this scheme failed due to the polymerization, destruction processes and rapid cleavage of such labile diazonium salts.

Moreover, it is well-known that presence of quinone moiety opens a possibility for further modifications allowing to construct polyfused heterocycles based on 1,4-addition reactions and cyclocondensations. Taking into account this fact, we decided to provide 1,4-addition of the thiourea to thienyl-quinone **3e** according to method originally proposed by Lau and Kestner.[20] It was found that formation of 2-oxobenzo[*d*][1,3]oxathiol-thiophene involved three stages: 1,4 addition of thiourea to protonated form of substituted quinone giving first thiouronium salt with the next cyclisation and hydrolyses. Finally, to generate chromenone cycle additional heating in toluene with *p*-toluenesulfonic acid catalysis was performed without isolation of product **B**. As a result polyfused 4*H*-[1,3]oxathiolo[5,4-*g*]thieno[2,3-*c*]chromene-4,8-dione system **5** was constructed.

Experimental

^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Varian Mercury 400 instrument (400MHz for ^{1}H, 125MHz for ^{13}C). The ^{1}H and ^{13}C chemical shifts were reported in

parts per million relative to tetramethylsilane or the deuterated solvent as an internal reference. Mass spectra were performed using Agilent 1100 series LC/MSD with an API-ES/APCI ionization mode and low-resolution electron impact mass spectra (EIMS) on an Agilent 6890N gas chromatograph equipped with a 5973N mass selective detector and a 7683B automatic liquid sampler (Agilent Technologies). The evolution of reactions and purity of the synthesized compounds were monitored chromatographically on Silufol UV-254 plates.

General procedure for the synthesis of aryl- and thienylquinones 3a-e

Appropriate amine **1** (0.02mol) was dissolved in concentrated hydrochloric acid (5mL) and ice (15g) was added. When the mixture was cooled to 0˚C, saturated sodium nitrite (1.73g; 0.025mol) aqueous solution was added keeping the temperature below 5˚C. After 10min, resinous sediment (in case it was formed) should be filtered. Filtrated solution of the diazonium salt was added dropwise into quinone (2.5g; 0.024mol), $AcONa{\cdot}3H_2O$ (6.84g; 0.045mol) water (150ml) suspension keeping the temperature at 15-20˚C. The reaction mixture was left stirring for 2hours . The formed solid product was filtered and recrystallized from ethanol or ethanol/DMF solution.

Methyl 2-(3,6-dioxocyclohexa-1,4-dienyl)benzoate (3a)

(This compound was previously reported by Honraedt at al. [14])**:** Yield: 86% as a light brown solid; mp 114–115 ºC; ^{1}H NMR (400MHz, DMSO-d_6): δ 7.98 (1H, d, *J* = 7.4Hz, H_{Ar}-6), 7.72 (1H, t, *J* = 7.4Hz, H_{Ar}-4), 7.62 (1H, t, *J* = 7.4Hz, H_{Ar}-5), 7.45 (1H, d, *J* = 7.4Hz, H_{Ar}-3), 6.98 (2H, br.s, $H_{Quinone}$), 6.83 (1H, s, $H_{Quinone}$), 3.70 (3H, s, MeO). ^{13}C NMR (125MHz, DMSO-d_6): δ 188.06 ($CO_{Quinone}$), 186.46 ($CO_{Quinone}$), 166.80 (*C*OOMe), 149.35 ($C_{Quinone}$), 137.35 (CH), 137.30 (CH), 134.89 (C_{Ar}-2), 133.44 (CH), 131.39 (CH), 131.04 (CH), 130.25 (CH), 130.20

(C_{Ar}-1), 130.08 (CH), 52.71 (OMe). MS (m/z): 243 (M^+ + 1). Anal. calcd. for $C_{14}H_{10}O_4$: C, 69.42; H, 4.16; found: C, 69.49; H, 4.25.

General procedure for the synthesis of 2-hydroxy-6H-benzo[c]chromen-6-ones 4a-d and 8-hydroxy-4H-thieno[2,3-c]chromen-4-one 4e

Method A

Sodium sulfide nonahydrate (1.44g; 0.006mol) was added to the solution of compound **3** (0.002mol) in ethanol (10ml) – water (2ml). The reaction mixture is heated at 60°C for 2hours . Solvent is evaporated under reduced pressure and the residue is extracted with dichloromethane. Dichloromethane is evaporated in vacuum, the solid product was recrystallized from ethanol or ethanol/DMF solution.

Method B

A solution of compound **3** (0.002mol) in glacial acetic acid (5ml) was added to the well-stirred mixture of zinc dust (0.13g; 0.01mol) in glacial acetic acid (5ml). After the mixture was refluxed for 30min, zinc compounds and excess of zinc dust were filtrated off. The filtrate was concentrated under reduced pressure to remove acetic acid and the residue was purified by recrystallization from ethanol or ethanol/DMF solution.

2-Hydroxy-6H-benzo[c]chromen-6-one (4a)

(This compound was previously reported by Engelman et al. [10] and Yang at al. [11, 12a])**:** Yield: 89% as a grey solid; mp 215–216 ºC; ^{1}H NMR (400MHz, DMSO-d_6) δ 9.72 (1H, s, OH), 8.22 (2H, br.s, H-10,7), 7.89 (1H, t, *J* = 7.7Hz, H-9), 7.63 (1H, t, *J* = 7.6Hz, H-8), 7.57 (1H, s, H-1), 7.23 (1H, d, *J* = 8.8Hz, H-4), 6.98 (1H, dd, *J* = 8.9, 2.8Hz, H-3). ^{13}C NMR

(125MHz, DMSO-d_6): δ 160.87 (COO), 154.81 (COH), 144.35 (*C*OC), 135.68 (CH), 134.74 (C-10a), 130.21 (CH), 129.61 (CH), 122.91 (CH), 121.03 (C-6a), 118.91 (CH), 118.63 (C-1a), 118.56 (CH), 108.64 (CH). MS (m/z): 213 (M^+ + 1). Anal. calcd. for $C_{13}H_8O_3$: C, 73.58; H, 3.80; found: C, 73.51; H, 3.75.

4H[1,3]Oxathiolo[5,4-g]thieno[2,3-c]chromene-4,8-dione (5)

To a solution of 0.15mol of thiourea in 100ml of 2N hydrochloric acid 0.1mol (g) of thienylquinone **3e** in 60ml of glacial acetic acid was added with stirring. The mixture was stirred at room temperature for 30min, during which time a mass of crystalline thiouronium salt precipitated. Upon heating on a steam bath, the salt re-dissolved to give a clear solution. The mixture was heated for 1 hr, then chilled in an ice bath until crystallization was complete. The solid was collected, washed with water, the resulted precipitate without recrystallization was dissolved in 50ml of toluene and *p*-TSA was added as a catalyst. The reaction mixture was heated under reflux for 4hours, then chilled at room temperature and washed with aqueous 2N NaOH solution. The toluene layer was collected and the solvent was evaporated under reduced pressure. Yield: 88% as a light purple solid; mp 252–253 ºC; ^{1}H-NMR (400MHz, DMSO-d_6): δ 8.43 (1H, d, *J* = 4.8Hz, H-2), 8.04 (1H, d, *J* = 4.8Hz, H-1), 7.78 (1H, d, *J* = 2.2Hz, H-10), 7.28 (1H, d, *J* = 2.3Hz, H-6). ^{13}C NMR (125MHz, DMSO-d_6): δ 171.43 (SCO), 158.02 (CO), 156.11 (C), 146.50 (CH), 145.25 (C), 139.65 (CH), 125.52 (C), 124.41 (C), 124.37 (C), 120.02 (C), 114.72 (CH), 111.82 (CH). MS (m/z): 277 (M^+ + 1). Anal. calcd. for $C_{12}H_4O_4S_2$: C, 52.17; H, 1.46; found: C, 52.05; H, 1.63.

Conclusion

In summary, we have described a simple efficient method for the synthesis of the substituted 6*H*-benzo[*c*]chromene-6-ones and 4*H*-thieno[2,3-*c*]chromen-4-one, which are suitable for the evaluation of biological activity and further drug discovery.

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References

[1] Sun, J.; Awakawa, T.; Noguchi, H.; Abe, I. Induced Production of Mycotoxins in an Endophytic Fungus from the Medicinal Plant *Datura stramonium* L. *Bioorg. Med. Chem. Lett.* **2012**, *22*(20), 6397–6400.

[2] Mazimba, O. Synthetic Protocols on 6h-Benzo[C]Chromen-6-Ones: A Review. *Turk. J. Chem.* **2016**, *40*, 1–27.

[3] Nemecek, G.; Cudaj, J.; Podlech, J. Revision of the Structure and Total Synthesis of Altenuisol. *Eur. J. Org. Chem.* **2012**, *20*, 3863–3870.

[4] Kym, P. R.; Kort, M. E.; Coghlan, M. J.; Moore, J. L.; Tang, R.; Ratajczyk, J. D.; Larson, D. P.; Elmore, S. W.; Pratt, J. K.; Stashko, M. A. et al. Nonsteroidal Selective Glucocorticoid Modulators: The Effect of C-10 Substitution on Receptor Selectivity and Functional Potency of 5-Allyl-2,5-dihydro-2,2,4-trimethyl-1*H*-[1]benzopyrano[3,4-*f*]quinolones. *J. Med. Chem.* **2003**, *46*, 1016–1030.

[5] Iaroshenko, V. O.; Ali, S.; Mkrtchyan, S.; Gevorgyan, A.; Babar, T. M.; Semeniuchenko, V.; Hassan, Z.; Villinger, A.; Langer, P. Design and Synthesis of Condensed Thienocoumarins by Suzuki–Miyaura Reaction/Lactonization Tandem Protocol. *Tetrahedron Lett.* **2012**, *53*(52), 7135–7139.

[6] McGee, L. R.; Confalone, P. N. On the Photobiology of the Gilvocarcins. Total Synthesis of Defucogilvocarcin V and a Related Photoactive Vinyl Phenol. *J. Org. Chem.* **1988**, *53*(16), 3695–3701.

[7] Appel, B.; Saleh, N.N.R.; Langer, P. Domino Reactions of 1,3-Bis-Silyl Enol Ethers with Benzopyrylium Triflates: Efficient Synthesis of Fluorescent 6*H*-Benzo[*c*]Chromen-6-Ones, Dibenzo[*c,d*]Chromen-6-Ones, and 2,3-Dihydro-1*H*-4,6-Dioxachrysen-5-Ones. *Chem. Eur. J.* **2006**, *12*, 1221–1236.

[8] Ray, S.; Patra, A.; Mal, D. Tandem Annulation Strategy for the Convergent Synthesis of Benzonaphthopyranones: Total Synthesis of Chartarin and O-Methylhayumicinone. *Tetrahedron* **2008**, *64*, 3253–3267.

[9] Ueberschaar, N.; Dahse, H.-M.; Bretschneider, T.; Hertweck, C. Rational Design of an Apoptosis-Inducing Photoreactive DNA Intercalator. *Angew. Chem. Int. Ed.* **2013**, *52*, 6185–6189.

[10] Engelman, K .L.; Feng, Y.; Ison, E. A. C–H Bond Functionalization of Benzoic Acid: Catalytic Synthesis of 2-Hydroxy-6H-Benzo[c]Chromen-6-Ones Using (Cp*IrCl2)2. *Organometallics* **2011**, *30*, 4572–4577.

[11] Yang, W.; Wang, S.; Zhang, Q.; Liua, Q.; Xu, X. Rh(III)-Catalyzed Oxidative C–H Bond Arylation with Hydroquinones: Sustainable Synthesis of Dibenzo[b,d]Pyran-6-Ones and Benzo[d]Naphtho[1,2-b]Pyran-6-Ones. *Chem. Commun.* **2015**, *51*, 661–664.

[12] a) Yang, W.; Wang, J.; Wei, Z., Zhang, Q.; Xu, X. Kinetic Control of Rh(III)-Catalyzed Annulation of C–H Bonds with Quinones: Chemoselective Synthesis of Hydrophenanthridinones and Phenanthridinones. *J. Org. Chem.*, **2016**, *81*(4), 1675–1680. (b) Qi, Z.; Li, X. Rh(III)-Catalyzed C–H Activation of Benzamides: Coupling with Quinones. *Chin. J. Catal.* **2015**, *36*, 48–56.

[13] Crespi, S.; Jäger, S.; König, B.; Fagnoni, M. A Photocatalytic Meerwein Approach to the Synthesis of Isochromanones and Isochromenones. *Eur. J. Org. Chem.*, **2017**, *15*, 2147–2153.

[14] Honraedt, A.; Callonnec, F. L;, Grognec, E. L; Fernandez, V.; Felpin, F.-X. C−H Arylation of Benzoquinone in Water through Aniline Activation: Synergistic Effect of Graphite-Supported Copper Oxide Nanoparticles. *J. Org. Chem.* **2013**, *78*(9), 4604–4609.

[15] Obushak, N. D.; Martyak, R. L.; Matiichuk V. S. Heterocycles Synthesis Based on Arylation Products of Unsaturated Compounds: XII.* Reactions of 2-Aryl-1,4-benzoquinones with Dithiol Compounds. *Russ. J. Org. Chem.* **2005**, *41*(5), 748–752.

[16] Martyak, R. L.; Obushak, N. D.; Matiichuk V. S. Synthesis of Heterocycles on the Basis of Arylation Products of Unsaturated Compounds: XX.* Reaction of 2-Aryl-1,4-Benzoquinones with Potassium O-Butyl Carbonodithioate. *Russ. J. Org. Chem.* **2010**, *46*(3), 394–398.

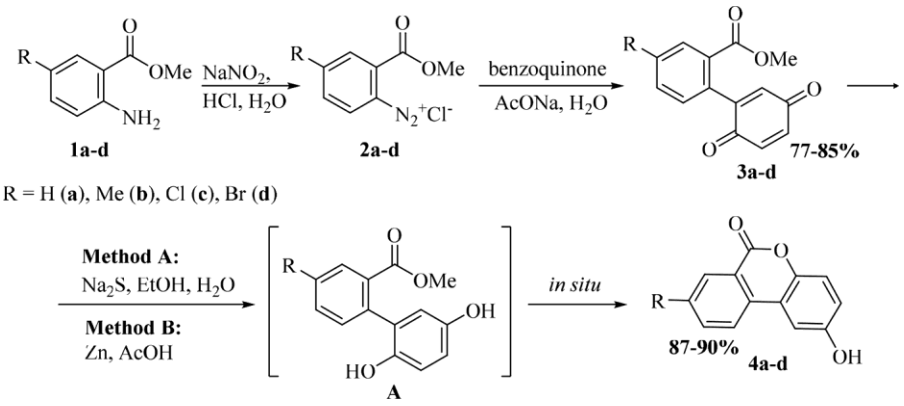
[17] Pokhodylo, N. T.; Shyyka, O. Y.; Obushak M. D. Facile and Efficient One-Pot Procedure for Thieno[2,3-*e*][1,2,3]Triazolo[1,5-*a*] Pyrimidines Preparation. *Synth. Commun.* **2014**, *44*(7), 1002–1006.

[18] Pokhodylo, N. T.; Shyyka, O. Y.; Obushak N. D. Ethyl 2-Aminothiophene-3-Carboxylates in the Synthesis of Isomeric Thienopyridines. *Chem. Heterocycl. Compd.* **2014**, *50*(12), 1748–1755.

[19] Pokhodylo, N. T.; Shyyka, O. Y.; Savka, R. D.; Obushak M. D. Novel Selected Tandem Transformations of the Amino and Carbonyl/Nitrile Groups in the Gewald Thiophenes. *Phosphorus Sulfur Silicon Relat Elem.* **2010**, *185*(10), 2092–2100.

[20] Lau, P. T. S.; Kestner, M. A. One- Step Synthesis of 5-Hydroxy-1,3-Benzoxathiol-2-Ones from Quinones and Thiourea. *J. Org. Chem.* **1968**, *33*(12), 4426–4431.

Scheme 1. Synthesis of 2-hydroxy-6H-benzo[c]chromen-6-ones **4a-d**.



Scheme 2. Synthesis of 4H-thieno[2,3-c]chromen-4-one 4e and 2-oxobenzo[d][1,3]oxathiol-thiophene **5**.