Microwave AssistedSynthesisof 2,3-Dihydro-4*H*-benzo[4,5]thiazolo[3,2-*a*]furo[2,3-*d*]pyrimidin-4-ones and 6,7-Dihydro-5*H*-furo[2,3-*d*]thiazolo[3,2-*a*]pyrimidin-5-ones Using $Mn(OAc)_3$

Aslı Ustalar, Mehmet Yilmaz

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Microwave Assisted Synthesis of 2,3-Dihydro-4*H*-benzo[4,5]thiazolo[3,2-*a*]furo[2,3-*d*]pyrimidin-4-ones and 6,7-Dihydro-5*H*-furo[2,3-*d*]thiazolo[3,2-*a*]pyrimidin-5-ones Using $Mn(OAc)_3$

Aslı Ustalar, Mehmet Yilmaz*

Department of Chemistry, Faculty of Arts and Sciences, Kocaeli University, 41380 Umuttepe, Kocaeli, Turkey

Abstract

2-Hydroxy-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-one **2a** and 7-hydroxy-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one **2b**, were obtained in high yields under mild conditions from the cyclization reactions of bis-(2,4,6-trichlorophenyl) malonate and 2-aminobenzothiazole or 2-aminothiazole, respectively. A new class of compounds, 2,3-dihydro-4*H*-benzo[4,5]thiazolo[3,2-*a*]furo[2,3-*d*]pyrimidin-4-ones and 6,7-dihydro-5*H*-furo[2,3-*d*]thiazolo[3,2-*a*]pyrimidin-5-ones, were synthesized *via* the microwave assisted radical addition of compounds **2a** and **2b** to various alkenes using manganese(III) acetate. A preliminary acetylcholine esterase (AchE) inhibition test of compound **4e** showed excellent (92%) inhibitory potential, comparable with the standard drug Donapezil®.

Keywords: manganese(III) acetate; radical addition; cyclization; microwave; single crystal X-ray analysis; AchE inhibition

E-mail: mehmet.yilmaz@kocaeli.edu.tr

Phone: +90-262-3032058, Fax: +90-262-3032003

Introduction

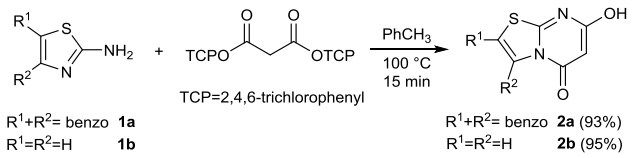
Heterocyclic ring systems such as thiazole, benzothiazole, benzothiazolopyrimidine, thiazolopyrimidine and dihydrofuran form the skeletal structures of molecules displaying a wide-range of biological activities. Thiazole and benzothiazole containing compounds have been reported to show antitumor, antimicrobial, anthelmintic, anti-leishmanial, anticonvulsant and anti-inflammatory effects.[1] Additionally, aminophenazole is used as an antidote for barbiturates and opiates,[2] chlormethiazole shows sedative and hypnotic effects[3] and amthamine is a histamine agonist.[4] Ritanserin[5] and setoperone[6] are thiazoloprymidine containing drugs used in the treatment of psychological diseases. Additionally, many

thiazolopyrimidine derivatives also show acetylcholine esterase inhibition,[7] antioxidant and antitumor activity[8] and anti-inflammatory, antimicrobial and antiviral[9] effects. Primidobenzothiazoles[10] and dihydrofuropyrimidines[11] show antibacterial, anti-fungal and anti-allergic activities.

It is known that transition metal salts (Mn^{+3}, Co^{+3}, Cu^{+2}, Ce^{+4}) which are able to transfer single electrons, form α-carbon radicals with enolizable functional groups and the addition of this radical to unsaturated systems can be used to generate new C-C bonds.[12] Among these metal salts, manganese(III) acetate[13] and cerium(IV) ammonium nitrate[14] are widely used. Our research group has reported the radical addition and cyclization of various active methylene compounds to unsaturated systems using manganese(III) acetate and cerium(IV) ammonium nitrate, resulting in the formation of functionalized dihydrofuran containing compounds.[13f-r, 14i-k] Herein, we report the $Mn(OAc)_3$ mediated radical addition of 2-hydroxy-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-one **2a** and 7-hydroxy-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one **2b** to conjugated alkenes **3a-c,e** and diene **3d** under microwave irradiation, leading to 2,3-dihydro-4*H*-benzo[4,5]thiazolo[3,2-*a*]furo[2,3-*d*]pyrimidin-4-one **4a-d** and 6,7-dihydro-5*H*-furo[2,3-*d*]thiazolo[3,2-*a*]pyrimidin-5-one **4e-i** derivatives in high yields.

Result and Discussion

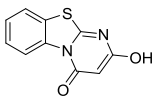
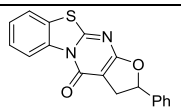
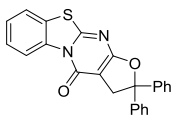
It was previously reported that the starting compounds, 2-hydroxy-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-one[15] **2a** and 7-hydroxy-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one[16] **2b**, could be synthesized using carbon suboxide in 83% and 90% yield, respectively. Herein, we used a modified method for the synthesis of these compounds.[17] For this purpose, 2-hydroxy-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-one **2a** (93%) and 7-hydroxy-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one **2b** (95%) were synthesized from the reaction of 2-aminobenzothiazole **1a** and 2-aminothiazole **1b**, respectively, with bis(2,4,6-trichlorophenyl)malonate[17] in toluene at 100 °C for 15 minutes.

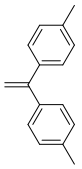
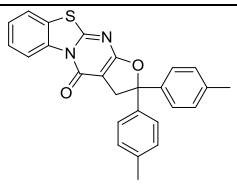
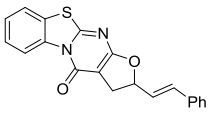
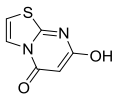
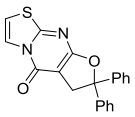
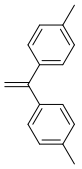
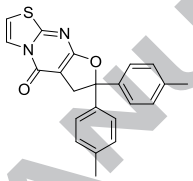
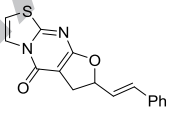
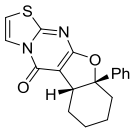
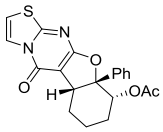


Scheme 1. Synthesis of 2-hydroxy-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-one **2a** and 7-hydroxy-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one **2b**.

The microwave assisted radical addition of various alkenes to benzothiazolopyrimidine **2a** or thiazolopyrimidine **2b**, mediated by $Mn(OAc)_3$, gave dihydrobenzothiazolofuropyrimidine **4a-d** and dihydrofurothiazolopyrimidine **4e-i** containing compounds, respectively. The best results were obtained at 150 °C, 350 W with 60 sec reaction time; all results are given in Table 1. While the reaction of 2-hydroxy-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-one **2a** with styrene **3a** gave dihydrofuran **4a** in 40% yield, the reaction of **2a** with 1,1-diphenylethylene **3b** gave **4b** in 90% yield. Similar results were obtained from the reactions of **2a** with 4,4'-(ethene-1,1-diyl)bis(methylbenzene) **3c** and (*E*)-1-phenyl-1,3-butadiene **3d**, to form dihydrofurans **4c** (65%) and **4d** (80%), respectively, in good yields. 7,7-Diphenyl-6,7-dihydro-5*H*-furo[2,3-*d*]thiazolo[3,2-*a*]pyrimidin-5-one (**4e**) was obtained in 95% yield from the reaction between 7-hydroxy-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one **2b** and **3b**. Additionally, the treatment of **2** with **3c** formed dihydrofuran **4f** in excellent yield (93%). Compound **4g** (75%) was obtained from the radical cyclization of **2b** with **3d**. The reaction between **2b** and phenylcyclohexene **3e** gave dihydrofuran **4h** and acetyloxylated-dihydrofuran **4i** in 43% and 22% yield, respectively. Compound **4i** was obtained as a single diastereomer and its structure determined by ^{1}H-NMR, ^{13}C-NMR, HSQC and COSY spectra. The configurations of compounds **4h** and **4i** were determined by NOESY spectra; in **4h** and **4i** a strong correlation was observed between the H-5b proton and the *ortho*-protons of the phenyl group. Based on these results, the Ph and H-5b protons are on the same plane for both compounds and the Ph and acetyloxy groups in compound **4i** are on different planes.

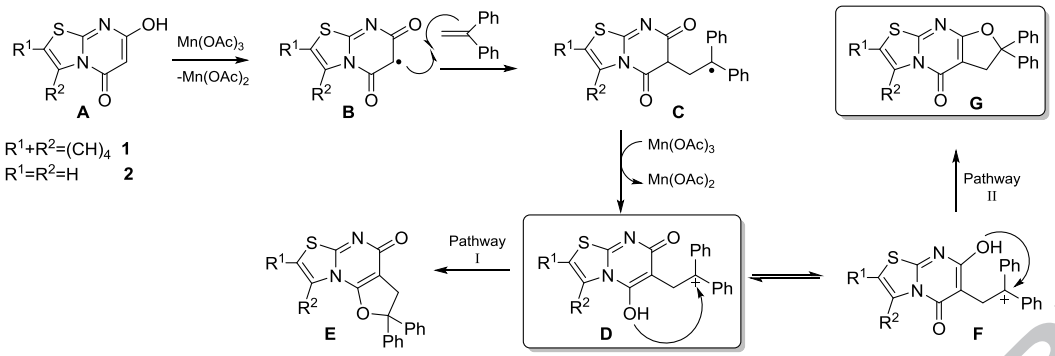
Table 1. Addition reactions of compounds **2a** and **2b** with alkenes (**3a-c,e**) and diene (**3d**).[a]

Entry	1,3-Dicarbonyl	Alkene	Dihydrofuran	Yield[b] (%)
1	 **2a**	 **3a**		**4a**, 40
2	**2a**	 **3b**		**4b**, 90

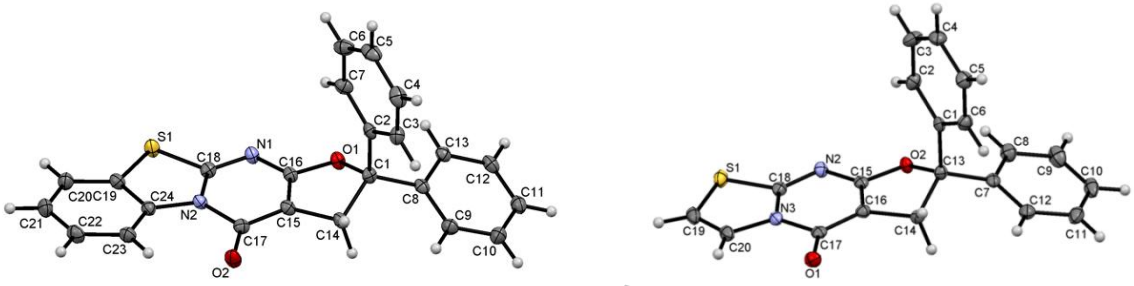
3	**2a**	 **3c**		**4c**, 65
4	**2a**	 **3d**		**4d**, 80
5	 **2b**	 **3b**		**4e**, 95
6	**2b**	 **3c**		**4f**, 93
7	**2b**	 **3d**		**4g**, 75
8	**2b**	 **3e**	 **4h**, 43	 **4i**, 22

[a] Reaction conditions: **2a** or **2b** (1 mmol), alkene or diene (1.2 mmol), $Mn(OAc)_3$ (2.5 mmol), acetic acid (10 mL), microwave irradiation 150 °C, 350 W, 60 s.
[b] Isolated yield based on the 1,3-dicarbonyl compound.

A proposed reaction mechanism is shown in Scheme 1. Initially, an α-carbon radical **B** is formed from the reaction of $Mn(OAc)_3$ with **A**. Intermediate **C** then forms from addition of the α-carbon radical to 1,1-diphenylethylene. Oxidation of the intermediate product to carbocation **D** with $Mn(OAc)_3$ and intramolecular cyclization of **D** forms the angular compound **E**. Alternatively, using the enolic form of **D**, intramolecular cyclization of **F** results in the formation of compound **G**. Judging by the single crystal X-ray analysis of compounds **4b**[18] and **4e**,[19] the cyclization step was determined to have followed pathway II (Scheme 1).



Scheme 2. Proposed mechanism for the formation of compounds **4a-i**.



Scheme 3. Molecular structure of compound **4b** and **4e**. Displacement ellipsoids are drawn at the 50% probability level. H-atoms are shown as small spheres of arbitrary radii. Only one molecule in the asymmetric unit cell is shown.

In the inhibition study on acetylcholine esterase using the Ellman method,[20] compound **4e** showed 92% inhibition which was comparable with the standard commercial drug Donapezil®.

Conclusion

As a result of this work, a new class of compounds were obtained under microwave irradiation by the $Mn(OAc)_3$ promoted addition of 2-hydroxy-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-one **2a** and 7-hydroxy-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one **2b** to various alkenes in high yields. Our studies on the synthesis of new dihydrobenzothiazolofuropyrimidine **4a-d** and dihydrofurothiazolopyrimidine **4e-i** compounds and our investigation of their biological activities are an ongoing process.

Acknowledgements

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Supplementary data

Copies of NMR spectra for all compounds, single crystal X-ray data for compounds **4b** and **4e** (CCDC numbers 997074 and 997072, respectively). Supplementary data and crystallographic data associated with this article can be found in the online version, at http://dx.doi.org/

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18. Crystal data of **4b**: empirical formula, $C_{24}H_{16}N_2O_2S$; formula weight, 396.45; crystal colour, colourless; crystal system, monoclinic; space group, P 1 21/n 1; temperature (K), 120(2); wavelength (Å), 071073; lattice parameter, a/Å, 7.9918(2); b/Å, 18.7230(4); c/Å, 24.8616(5);α(°), 90; β(°), 95.2181(12); γ(°), 90; crystal size (mm), 0.050 x 0.080 x 0.120; *V* (Å^3), 3704.64(14); *Z*, 8; ρ_{calcd} (g.cm^{-3}), 1.422; μ (mm^{-1}), 0.199; *F*(000), 1648; θ range for data collection(°), 27.10; *h*/*k*/*l*, -10<=h<=10, -24<=k<=24, -31<=l<=31; R(reflections), 55115; T_{min} and T_{max} , 0.9900 and 0.9760; wR2, 0.01078; Crystallographic data (excluding structure data factors) for the structures in this letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publicatıon number CCDC 997074. Copies of the data can be obtained free of charge on an application to CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK [fax: +44 1223336033 or e-mail: deposit@ccdc.cam.ac.uk].
19. Crystal data of **4e**: empirical formula, $C_{20}H_{14}N_2O_2S$; formula weight, 346.39; crystal system, monoclinic; space group, P 1 21/c 1; temperature (K), 120(2); wavelength (Å), 071073; lattice parameter, a/Å, 14.7987(6); b/Å, 9.2610(3); c/Å, 11.7875(4); α(°), 90; β(°), 90.292(12); γ(°), 90; crystal size (mm), 0.086 x 0.129 x 0.320; *V* (Å^3), 1615.46(10); *Z*, 4; ρ_{calcd} (g.cm^{-3}), 1.424; μ (mm^{-1}), 0.217; *F*(000), 720; θ range for data collection(°), 27.48; *h*/*k*/*l*, -15<=h<=19, -11<=k<=12, -15<=l<=15; R(reflections), 16955; T_{min} and T_{max} , 0.9820 and 0.9340; wR2, 0.0946; Crystallographic data (excluding structure data factors) for the structures in this letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publicatıon number CCDC 997072. Copies of the data can be obtained free of charge on an application to CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK [fax: +44 1223336033 or e-mail: deposit@ccdc.cam.ac.uk].

20. Ellman, G. L.; Courtney, K. D.; Andres Jr, V.; Featherstone, R. M. *Biochem. Pharmacol.* **1961**, *7*, 90-95.

Highlights

Compounds **2a** and **2b** were obtained in high yields under mild reaction conditions.

Radical addition of **2a** and **2b** to various alkenes using $Mn(OAc)_3$ was achieved.

New classes of compounds (**4a-i**) were synthesized under microwave irradiation.

Graphical Abstract

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Microwave Assisted Synthesis of 2,3-Dihydro-4*H*-benzo [4,5]thiazolo[3,2-*a*]furo[2,3-*d*]pyrimidin-4-ones and 6,7-Dihydro-5*H*-furo[2,3-*d*]thiazolo[3,2-*a*]pyrimidin-5-ones Using $Mn(OAc)_3$

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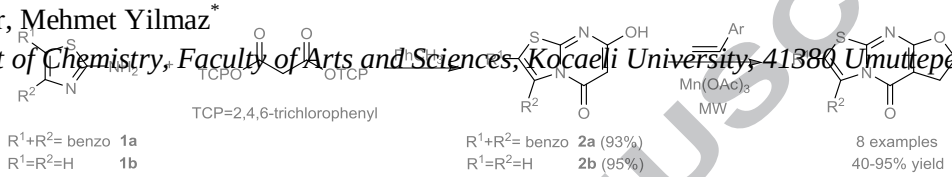
Aslı Ustalar, Mehmet Yilmaz*
Department of Chemistry, Faculty of Arts and Sciences, Kocaeli University, 41380 Umuttepe, Kocaeli-Turkey



R^1+R^2= benzo **1a**
R^1=R^2=H **1b**

R^1+R^2= benzo **2a** (93%)
R^1=R^2=H **2b** (95%)

8 examples
40-95% yield