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Microwave Induced Synthesis of Ferrocenyl Substituted 1,2,4-*s*-Triazolo[3,4-*b*]-1,3,4-thiadiazoles

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Summary. 5-Substituted 4-amino-3-mercapto-1,2,4-*s*-triazoles were synthesized from their corresponding hydrazides. Their condensation with ferrocene carboxylic acid in presence of phosphorus oxychloride under microwave irradiation afforded 3-substituted 6-ferrocenyl-1,2,4,-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles. All new compounds were characterized on the basis of analytical and spectroscopic data. Reaction rates and yields were considerably enhanced using microwaves.

Keywords. Triazole; Thiadiazole; Ferrocenyl; Microwaves.

Mikrowelleninduzierte Synthese von ferrocenylsubstituierten 1,2,4-*s*-Triazolo[3,4-b]-1,3,4-thiadiazolen

Zusammenfassung. In Stellung 5 substituierte 4-Amino-3-mercapto-1,2,4-*s*-triazole wurden aus den entsprechenden Hydraziden dargestellt. Ihre Kondensation mit Ferrocencarbonsäure in Gegenwart von Phosphoroxychlorid unter Mikrowellenbestrahlung ergab in Position 3 substituierte 6-Ferrocenyl-1,2,4-*s*-triazolo[3,4-*b*]-1,3,4-thiadozole. Alle neuen Verbindungen wurden durch ihre analytischen und spektroskopischen Daten charakterisiert. Reaktionsgeschwindigkeiten und Ausbeuten wurden durch die Verwendung von Mikrowellen deutlich erhöht.

Introduction

Tetrazole, thiadiazole, quinoline, and indole derivatives are well known for their significant biological activities [1–4]. A large number of 1,2,4-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles has been reported to exhibit various biological activities [5–6]. Some thiadiazole derivatives have found application as antitumour agents, pesticides, dyes lubricants, and analytical reagents [7].

Nothing has been reported so far on the synthesis of 1,2,4,-*s*-triazolo[3,4-*b*]1,3,4-thiadiazoles incorporating the ferrocenyl moiety using microwave irradiation. The importance of MORE (microwave induced organic reaction enhancement) [8] and the versatile biological activity of 1,2,4-*s*-triazolo[3,4-b]-1,3,4-thiadiazoles prompted us to report a new microwave induced method for the

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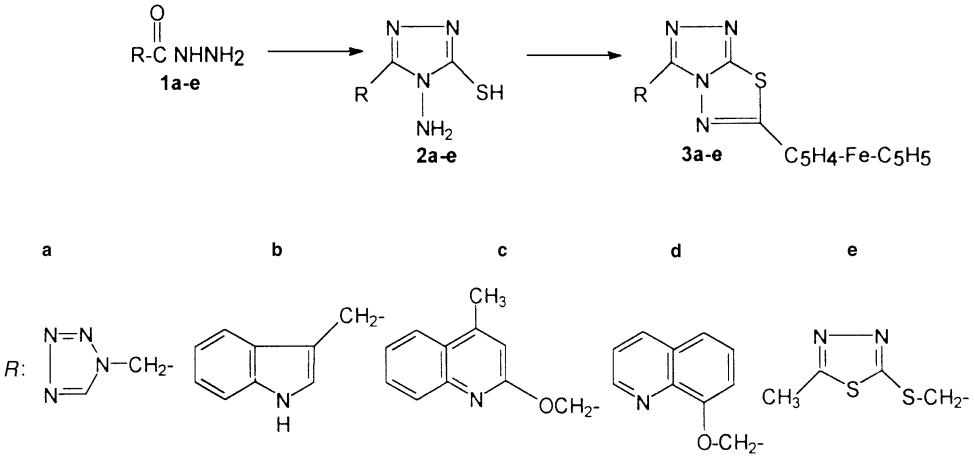
synthesis of some new nitrogen bridgehead heterocycles, potential antimicrobial agents.

Results and Discussion

Triazoles **2a–e** were synthesized from their corresponding hydrazides **1a–e** *via* potassium dithiocarbazate derivaties using an established method [9]. Under microwave irradiation, cyclocondensation of ferrocene carboxylic acid with the bifunctional triazoles **2a–e** afforded the bridgehead nitrogen heterocycles **3a–e** within 3–4 min (Scheme 1). A drastic reduction in reaction time was thus observed due to the rapid heating capability of microwaves.



Scheme 1

The structures of the triazoles **2a–e** were established on the basis of analytical and spectroscopic data. They showed common absorption bands at 3330, 3160 (–NH), and 1510–1620 (C=N) cm^{-1}, and their ^1H NMR spectra confirmed the presence of $-NH_2$ and –SH protons (two peaks at $\delta = 4.5$–4.8 (NH_2) and 12.8–13.2 (–SH) ppm, exchangable with D_2O). Other analytical and spectroscopic data are given in experimental section.

The IR data of the title compounds **3a–e** confirmed the condensation of ferrocene carboxylic acid with the bifunctional triazoles by the disappearence of the bands at 3330, and 3160 cm^{-1} (NH). The absorption bands at 1260–1280 cm^{-1} were assigned to N–N=C, and bands at 1510–1620 cm^{-1} suggest the presence of C=N. The bands at 3080, 1435, 820, 500, and 480 cm^{-1} correspond to ν_{C-H}, $\nu_{C=C}$, ν_{C-H}, $\nu_{Fe-C_5H_5}$, and $\nu_{C_5H_5}$ [10]. The ^1H NMR spectra of **3a–e** displayed ferrocenyl proton signals at $\delta = 4.2$ (5H), 4.5 (2H), and 4.8 (2H) ppm. The disappearence of the signals at 12.8–13.2 (SH) and 4.5–4.8 (NH_2) ppm confirmed that the reaction had occurred. The band at 285 nm in the UV spectra **3a–e** was bathochromically shifted compared to the parent compound 1,2,4-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazole which shows an absorption maximum at 251 nm [11]. In addition, there is a band at about 500 nm, which is characteristic of the ferrocene moiety.

Experimental

Melting points were determined by means of a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra KBr pellets were recorded on a Perkin-Elmer spectrophotomer model 599. ^{1}H NMR were recorded on α Perkin-Elmer R-32 (90 MHz) instrument using *TMS* as internal standard. Elemental analyses were determined by means of a Heraeus CHN rapid analyszer; their results agreed satisfactorily with the calculated values.

With exception of **1b** (Aldrich), compounds **1a**–**1e** were prepared according to Refs. [12–15], **2a**–**2e** according to Ref. [9] from **1a**–**1e**.

General procedure for the microwave induced synthesis of 3-substituted 6-ferrocenyl-1,2,4-s-triazolo[3,4-b]-1,3,4-thiadiazoles **3a**–**e**

A mixture of 0.01 mol triazole, 0.01 mol ferrocene carboxylic acid, and 5 ml $POCl_3$ were mixed in a 100 ml beaker. The beaker was kept in a water bath and zapped [16] inside a microwave oven (560 W) for a period of 3–4 min at 2450 MHz, The reaction mixture was cooled poured onto crushed ice, and neutralized with $NaHCO_3$. The product was collected by filtration, washed with H_2O, dried under vaccum at 50°C, and recrystallized from a mixture of CH_3OH and $CHCl_3$.

3-(1-(Tetrazol-1′-yl)methyl)-6-ferrocenyl-1,2,4-s-triazolo[3,4-b]-1,3,4-thiadiazole
(**3a**; $C_{15}H_{12}N_8SFe$)

Yield: 84% m.p.: 256–258°C; ^{1}H NMR (*DMSO*-d_6+$CDCl_3$ δ. 90 MHz): 4.12 (s, 5H, C_5H_5), 4.5 (t, $J = 1.55$ Hz, 2H, C_5H_4) 4.75 (t, $J = 1.55$ Hz, 2H, C_5H_4), 6.4 (s, 2H, CH_2), 9.5 (s, 1H, 5′-H) ppm; IR (KBr): $\nu = 3050$, 1610, 1430, 1270, 820, 510 cm^{-1}; UV/Vis (CH_3OH); λ_{max} (logε) = 280 (4.12), 502 (3.2) nm.

3-(1-(Indol-3′-yl)-methyl)-6-ferrocenyl-1,2,4-s-triazolo[3,4-b]-1,3,4-thiadiazole
(**3b**; $C_{22}H_{17}N_5SFe$)

Yield: 81%; m.p.: 198–199°C; ^{1}H NMR (*DMSO*-d_6+$CDCl_3$, δ, 90 MHz): 3.45 (s, 2H, CH_2) 4.24 (s, 5H, C_5H_5), 4.56 (t, $J = 1.56$ Hz, 2H, C_5H_4), 4.80 (t, $J = 1.56$ Hz, 2H, C_5H_4), 7.2–7.9 (m, 5H, Ar-H), 8.8 (br s, 1H, NH) ppm; IR (KBr): $\nu = 3070$, 1580, 1430, 1260, 810, 505 cm^{-1}; UV/Vis (CH_3OH): λ_{max} (log ε) = 287 (4.04), 495 (4.60).

3-(1-(4′Methyl-quinolin-2′-yloxy)-methyl)-6-ferrocenyl-1,2,4-s-triazolo[3,4-b]-1,3,4-thiadiazole)
(**3c**: $C_{24}H_{19}N_5OSFe$)

Yield: 85%; m.p.: 247–248°C, ^{1}H NMR (*DMSO*-d_6+$CDCl_3$, δ, 90 MHz): 2.4 (s, 3H, 4′-CH_3) 4.28 (s, 5H, C_5H_5), 4.60 (t, $J = 1.55$ Hz, 2H, C_5H_4), 4.82 (t, $J = 1.55$ Hz, 2H, C_5H_4), 5.45 (s, 2H, OCH_2), 7.2–7.7 (m, 5H, Ar-H) ppm; IR (KBr): $\nu = 3080$, 1570, 1440, 1250, 820, 510 cm^{-1}; UV/Vis (CH_3OH): λ_{max} (logε) = 275 (4.26), 512 (4.3).

3-(1-(Quinolin-8′-yloxy)-methyl)-6-ferrocenyl-1,2,4-s-triazolo[3,4-b]-1,3,4-thiadiazole
(**3d**; $C_{23}H_{17}N_5OSFe$)

Yield: 86%; m.p.: 242–243°C; ^{1}H NMR (*DMSO*-d_6+$CDCl_3$, δ, 90 MHz): 4.28 (s, 5H, C_5H_5) 4.58 (t, $J = 1.56$ Hz, 2H, C_5H_4), 4.80 (t, $J = 1.56$ Hz, 2H, C_5H_4), 5.45 (s, 2H, OCH_2), 7.3–7.9 (m, 6H, Ar-H) ppm; IR (KBr): $\nu = 3070$, 1580, 1440, 1270, 800, 505 cm^{-1}; UV/Vis (CH_3OH): λ_{max} (logε) = 285 (4.06), 510 (4.1) nm.

3-(1-(5′-Methyl-1′,3′,4′-thiadiazol-2′-ylthio)-methyl)-6-ferrocenyl-1,2,4-s-triazolo[3,4-b]-1,3,4-thiadiazole (**3e**; $C_{17}H_{14}N_6S_3Fe$)

Yield: 81%; m.p.: 154–155°C; ^{1}H NMR (*DMSO*-d_6+$CDCl_3$, δ, 90 MHz): 2.70 (s, 3H, 5′-CH_3) 4.20 (s, 5H, C_5H_5) 4.52 (t, $J = 1.57$ Hz, 2H, C_5H_4), 4.70 (s, 2H, SCH_2), 4.86 (t, $J = 1.57$ Hz, 2H, C_5H_4) ppm: IR (KBr): $\nu = 3080$, 1570, 1430, 1270, 810, 505 cm^{-1}; UV/Vis (CH_3OH): λ_{max} (logε) = 290 (4.18), 505 (3.4) nm.

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