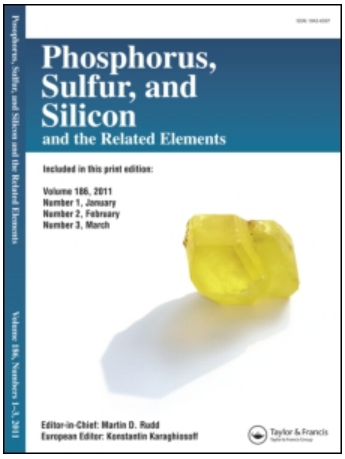

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Abdolali Alizadeh[a]; Sadegh Rostamnia[a]; Qasem Oskueyan[a]
[a] Department of Chemistry, Tarbiat Modares University, Tehran, Iran

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Facile and Rapid Synthesis of 4,5-Dihydrothiazol-2-ylamine Derivatives via Reaction Between Thiourea and Diaroylacetylenes

Abdolali Alizadeh, Sadegh Rostamnia, and Qasem Oskueyan
Department of Chemistry, Tarbiat Modares University, Tehran, Iran

Heterocyclic systems 4,5-dihydrothiazol-2-ylamine derivatives are synthesized via an intramolecular thioiminoformamide annulation reaction.

Keywords Dibenzoylacetylene (DBA); heterocyclic ring; 1,3-thiazol-2-amine; thiourea

INTRODUCTION

With regard to green chemistry, atom-efficient transformations of readily available starting materials into complex organic building blocks have become increasingly important.[1] Heterocyclic compounds have attracted considerable attention in the field of advanced materials as well as biologically active compounds.[2] Thiazoles are an important class of *S*,*N*-containing heterocycles, which were identified as such over a century ago.[3] Thiazoles and their derivatives are found to be associated with various biological activities such as antibacterial, antifungal, and anti-inflammatory activities.[4] Also heterocycles containing 2-aminothiazoles are found as urokinase inhibitors.[5]

In the context of our ongoing studies on heterocycles,[6*a*–*d*] we report herein a rapid procedure for the synthesis of 4,5-dihydrothiazol-2-ylamine derivatives.

RESULTS AND DISCUSSION

The reaction of thiourea with diaroylacetylene **1** proceeds in acetone at –10°C to produce 2-[2-amino-4-hydroxy-4-aryl-1,3-thiazol-5(4*H*)-yliden]-1-aryl-1-ethanone derivatives **2** in 85–90% yields (Table I).

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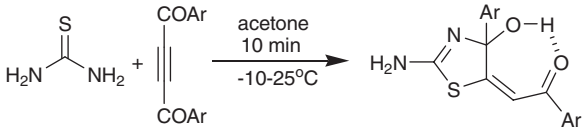
Address correspondence to Abdolali Alizadeh, Department of Chemistry, Tarbiat Modares University, P.O. Box 14115-175, Tehran, Iran. E-mail: aalizadeh@modares.ac.ir

TABLE I Reaction Between Thiourea and Diaroylacetylene

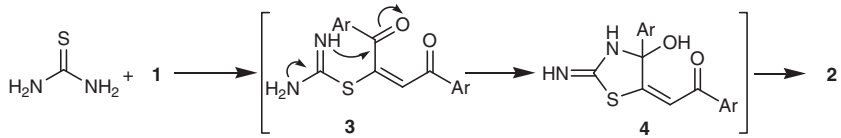


1 2

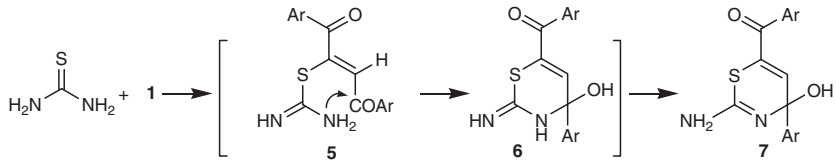
2	Ar	% Yield of 2
a	*p*-MeO-C_6H_4	85
b	Ph	90

The structures of compounds **2a** and **2b** were deduced from their elemental analysis, IR, and high-field ^{1}H and ^{13}C NMR spectra. The mass spectrum of **2a** displayed the molecular ion (MC) peak at*m/z* 370, which is consistent with the 1:1 adduct of 1,4-bis(4-methoxyphenyl)-2-butyne-1,4-dione and thiourea. The ^{1}H NMR spectrum of **2a** exhibited four single sharp singlets readily recognized as arising from methoxy ($\delta = 3.64$ and 3.80 ppm), OH ($\delta = 7.64$ ppm) protons, and a vinylic CH ($\delta = 7.32$ ppm). The OH H-atom at ($\delta = 7.64$ ppm) was a sharp and deshielded signal as a result of intramolecular H-bonding. The aryl moiety gave rise to characteristic signals in the aromatic region of the spectrum. The ^{1}H decoupled ^{13}C NMR spectrum of **2a** showed 15 distinct resonances in agreement with the 2-[2-amino-4-hydroxy-4-(4-methoxyphenyl)-1,3-thiazol-5(4*H*)-yliden]-1-(4-methoxyphenyl)-1-ethanone structure. Partial assignment of these resonances is given in the Experimental section. The ^{1}H and ^{13}C NMR spectra of compound **2b** are similar to those of **2a**, except for the aromatic moiety, and the OMe groups, which exhibit characteristic signals with appropriate chemical shifts (see the Experimental section).

Based on the well-established chemistry of thiourea addition as nuclephilic, and also electrophilic property of acetylene,[6–13] a possible mechanism of the reaction between thiourea and diaroylacetylenes is proposed in Scheme 1.



SCHEME 1 Proposed mechanism for the formation of compound **2**.



SCHEME 2

Based on the chemistry of thiourea and diaroylacetylene,[6–13] it is reasonable to assume that **2** results from the initial addition of thiourea to diaroylacetylene from the sulfur atom to produce 1-(3-[amino(imino)methyl]thio-4-oxo-4-aryl-2-butenoyl)aryl as an intermediate. Then, the thioiminoformamide **3**, based on an intramolecular annulation procedure, produced **2** (see Scheme 1).

A cyclic six-membered ring structure such as **7** is unlikely, because if compound **2** had a cyclic structure as in **7** (Scheme 2), then we would not observe intramolecular hydrogen bonding. Moreover, it is reported in the literature that the reaction of 1-aryl-3-arylcarbonylthioureas with dialkyl acetylenedicarboxylates in CH_2Cl_2 at room temperature leads to alkyl 2-[2-(arylcarbonylimino)-3-aryl-4-oxo-1,3-thiazolan-5-ylidene]-acetates in good yields.[7]

CONCLUSION

In conclusion, the present method carries the advantage that, not only is the reaction performed under neutral conditions, but also the substances can be mixed without any activation or modification. Also, using this method provides a route for the synthesis of a heterocyclic system using easily available precursors and reagents under very mild conditions.

EXPERIMENTAL

Diaroylacetylenes were prepared according to the procedure in the literature.[14,15] Thiourea was obtained from Fluka (Switzerland) and used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H and N were performed using a Heraeus CHN–O–Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 70 eV. ^1H and ^{13}C NMR spectra were measured (DMSO-d_6 solution) with a Bruker DRX-500 AVANCE

spectrometer at 500.13 and 125.7 MHz, respectively. IR spectra were recorded on a Shimadzu IR-460 spectrometer.

General Procedure

To a magnetically stirred solution of 0.15 g of thiourea (2 mmol)) in 4 mL of dry acetone, a solution of 0.47 g of dibenzoylacetylene (2 mmol) in 3 mL of dry acetone at –10°C was added dropwise over 3 min. The reaction was allowed to warm to room temperature and stirred for 10 min. The obtained solid powder was filtered off and washed with cooled acetone.

2-[2-Amino-4-hydroxy-4-(4-methoxyphenyl)-1,3-thiazol-5 (4*H*)-yliden]-1-(4-methoxyphenyl)-1-ethanone (2a)

White powder, mp = 142°C dec, yield 0.63 g, 85%. IR (KBr) (ν_{max} cm^{-1}): 3390 (OH), 3305 and 3210 (NH_2), 1645 (C=O), 1590 (C=N), 1505 and 1448 (Ar), 1285 and 1248 (C-N). MS, *m/z* (%): 370 (M^+, 2), 354 (5), 219 (100), 177 (36), 135 (53), 77 (34). Anal. Calcd. for $C_{19}H_{18}N_2O_4S$ (370.42): C, 61.61; H, 4.90; N, 7.56%. Found: C, 61.60; H, 5.10; N, 8.00. ^{1}H NMR (500.13 MHz, DMSO-d_6): δ_H = 3.64 (3 H, s, OMe), 3.80 (3 H, s, OMe), 6.74 (2 H, d, $^3J_{HH}$ = 8.7 Hz, 2 CH of Ar), 6.90 (2 H, br, NH_2), 6.96 (2 H, d, $^3J_{HH}$ = 8.9 Hz, 2 CH of Ar), 7.30 (2 H, d, $^3J_{HH}$ = 8.7 Hz, 2 CH of Ar), 7.32 (1 H, s, C=CH), 7.64 (1 H, s, OH), 7.88 (2 H, d, $^3J_{HH}$ = 8.9 Hz, 2 CH of Ar). ^{13}C NMR (125.7 MHz, DMSO–d_6): δ_C = 54.85 (OMe), 55.53 (OMe), 106.12 (*C*-OH), 112.73 (2 CH of Ar), 113.68 (SC= *C*H), 113.94 (2 CH of Ar), 125.80 (2 CH of Ar), 129.73 (C_{ipso}-C-OH), 131.05 (2 CH of Ar), 136.59 (C_{ipso}-CO), 151.14 (S*C* =CH), 158.18 (C_{ipso}-OMe), 163.48 (C_{ipso}-OMe), 173.47 (S-*C* =N), 187.07 (CO).

2-[2-Amino-4-hydroxy-4-phenyl-1,3-thiazol-5(4*H*)-yliden] -1-phenyl-1-ethanone (2b)

White powder, mp = 151°C dec, yield 0.56 g, 90%. IR (KBr) (ν_{max} cm^{-1}): 3345 (OH), 3282 and 3220 (NH_2), 1675 (C=O), 1640 (C=N), 1630 (C=C), 1590 and 1481 (Ar), 1235 and 1017 (C-N). MS, *m/z* (%): 310 (M^+, 8), 292 (11), 268 (13), 233 (23), 189 (53), 163 (79), (147 (34), 105 (94), 77 (100), 51 (30), 43 (28). Anal. Calcd. for $C_{17}H_{14}N_2O_2S$ (310.37): C, 65.79; H, 4.55; N, 9.03%. Found: C, 66.00; H, 4.50; N, 9.10%. ^{1}H NMR (500.13 MHz, DMSO-d_6): δ_H = 7.03–7.13, 7.40–7.44 and 7.80–7.86 (10 H, m, 10 CH of Ph), 7.20 (2 H, s, NH_2), 7.57 (1 H, s, C=CH), 7.67 (1 H, s, OH). ^{13}C NMR (125.7 MHz, d_6-DMSO): δ_C = 106.31 (C-OH), 113.96

(SC= *C*H), 124.53 (2 CH of Ph), 126.99 (CH of Ph), 127.37 (2 CH of Ph), 128.40 (2 CH of Ph), 128.59 (2 CH of Ph), 133.34 (CH of Ph) 136.96 (C_{ipso}-COH), 144.15 (C_{ipso}-CO), 151.75 (S*C* =CH), 173.99 (S-*C* =N), 188.54 (CO).

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