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Proceeding Paper

Transamination of 3-[(Dimethylamino)methylidene]-5-arylfuran-2(3*H*)-thiones with the Participation of 1,2-Phenylenediamine

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Abstract: Synthesis of 3-[((2-aminophenyl)amino)methylidene]furan-2(3*H*)-thiones was carried out by transamination reaction of 5-arylfuran-2(3*H*)-thiones under the influence of 1,2-phenylenediamine. A probable scheme of their formation was proposed. Configurational features of the obtained compounds were established on the basis of IR and NMR spectroscopy data, as well as using the NOESY 2D experiment.

Keywords: furan-2(3*H*)-thiones; 1,2-phenylenediamine; transamination reaction

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1. Introduction

Dimethylaminomethylidene derivatives of various classes of compounds are universal platform reagents in the synthesis of multifunctional heterocyclic compounds. The presence of several reaction centers determines participation in both addition and cyclocondensation reactions with nucleophilic reagents [1–4].

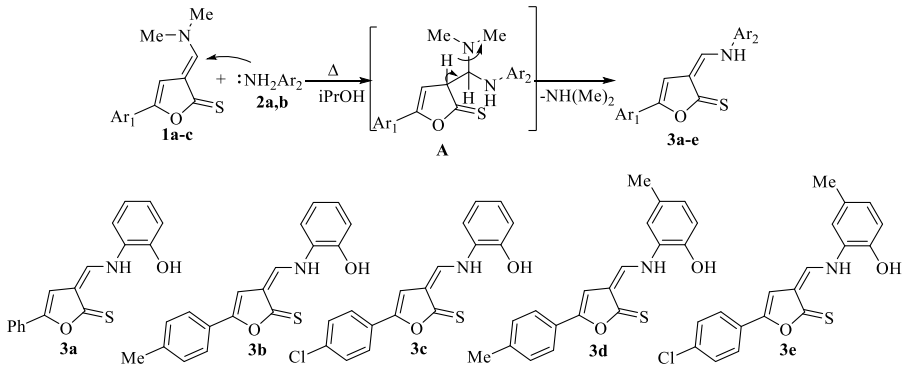
Dimethylaminomethylidene derivatives act as highly effective intermediates in multicomponent reactions, allowing the construction of polyheterocycles, which are promising compounds exhibiting antibacterial [5] and antitumor [6,7] activity against various lines of cancer cells.

2. Results and Discussion

Previously, aminomethylidene structures were obtained by direct amination reaction based on the interaction of 5-arylfuran-2(3*H*)-ones, orthoester and heterocyclic amines [8]. The most well-known method for constructing aminomethylidene compounds is the transamination reaction of compounds containing a dimethylaminomethylidene fragment.

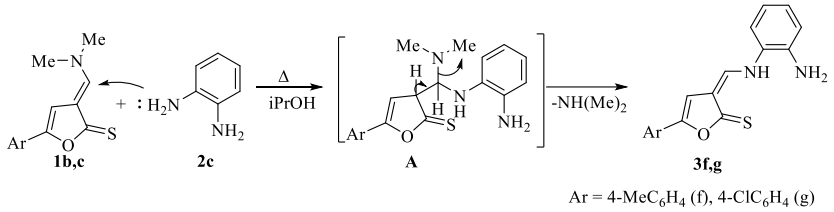
2.1. Synthesis of 3-[((2-Aminophenyl)amino)methylidene]-5-arylfuran-2(3H)-thiones

We were the first to develop conditions for the transamination of 3-[(dimethylamino)methylidene]-5-arylfuran-2(3*H*)-thiones and introduced aromatic amines containing electron-donating substituents into the reaction [9].



Scheme 1. General scheme for the synthesis of 3-aminomethylenefuran-2(3*H*)-ones **3a–e**.

In continuation of the work on expanding the range of aminomethylidenefuran-2(3*H*)-thiones, we introduced 1,2-phenylenediamine as an amino component into the transamination reaction. Boiling in isopropyl alcohol was chosen as the optimal conditions, similar to the reaction conditions with 2-aminophenol and 2-amino-4-methylphenol. The reaction resulted in 3-[((2-aminophenyl)amino)methylidene]-5-arylfuran-2(3*H*)-thiones **3f**,**g**.



Scheme 2. Synthesis of 3-[((2-aminophenyl)amino)methylidene]-5-arylfuran-2(3*H*)-thiones **3f**,**g**.

2.2. Structure of 3-[((2-Aminophenyl)amino)methylidene]-5-arylfuran-2(3H)-thiones **3f**,**g**

The structure of the obtained compounds was established on the basis of IR and NMR spectroscopy data. The IR spectrum of compounds **3f**,**g** contains absorption bands of the thiocarbonyl group at 1091–1094 cm^{-1}, as well as stretching vibrations of the NH group, which appear in the region of 3280–3282 cm^{-1}, and stretching vibrations of the double C=C bond are observed at 1655–1657 cm^{-1}, which proves the existence of the final products **3f**,**g** in the aminomethylidene thione form.

Using NMR spectroscopy, it was established that transamination proceeds with the formation of compounds **3f**,**g** in the form of an isomer with the *Z*-configuration of the double C=C bond. This can probably be proven by the shift of the NH-group proton signal to the region of weak fields (13.11, 13.16 ppm for **3f**,**g**, respectively), as well as by the observation of the spin-spin interaction constants on the H-bonded proton (J = 12.0 Hz), which confirms the existence of the obtained compounds **3f**,**g** in the *cis*-enamine configuration with an intramolecular hydrogen bond of the NH···S type.

Using the example of 3-[((2-aminophenyl)amino)methylidene]-5-(4-chlorophenyl)furan-2(3*H*)-thione 3g, the NOESY 2D experiment showed the spatial proximity of the protons of the NH group and NH_2 group, which corresponds to the cross peak at 5.13/13.16 ppm, and also showed the absence of a correlation between the proton of the furan-2(3*H*)-thione and NH group, which additionally indicates in favor of the *Z*-isomer (Figure 1).

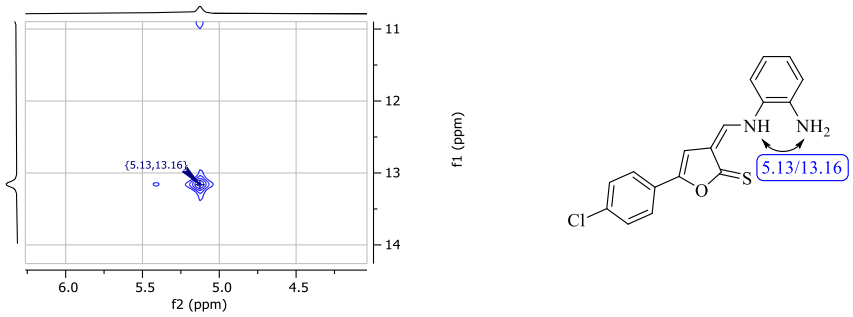


Figure 1. Fragment of NOESY 2D spectra of compound **3g**.

3. Material and Methods

3.1. Physical Measurements

IR spectra were recorded on a Nicolet 6700 Fourier spectrophotometer (Thermo Scientific, Waltham, MA, USA) in the range of 4000–40 cm^{-1} in KBr tablets. The ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra in DMSO-d_6 were recorded with a Varian (Agilent) 400 spectrometer (Agilent Technologies, Santa Clara, CA, USA), and the internal standard was TMS. Chemical shifts (δ) are reported in ppm. Elemental analysis was performed on a CHNS analyzer "Elementar Vario MICRO cube" (Elementar Analysensysteme GmbH, Hanau, Germany). Melting points were determined on a *Stuart*™ SMP10 melting point apparatus (Cole-Parmer, Beacon Road, Stone, Staffordshire, ST15 OSA, UK). The progress of the reaction and the purity of the synthesized compounds were monitored by TLC on ALUGRAM® SIL G UV254 plates (MACHEREY-NAGEL GmbH & Co. KG, Düren, Germany), a hexane-ethyl acetate-acetone (2:2:1) mixture was the eluent.

3.2. Synthesis and Characterization of Compounds **3f**,**g**

A mixture of 1 mmol of the corresponding 3-[(dimethylamino)methylidene]-5-arylfuran-2(3*H*)-thione **1b**,**c** and 1 mmol of 1,2-phenylenediamine **2c** in 5 mL of isopropanol was boiled for 40 min. The reaction mixture was evaporated on a rotary evaporator, the residue was triturated with water and filtered. It was recrystallized from toluene and dried in air.

(Z)-3-[((2-aminophenyl)amino)methylidene]-5-(p-tolyl)furan-2(3H)-thione **3f**

Red crystals (toluene), yield 0.22 g (72%), mp 200–202 °C; FTIR, ν, cm^{-1}: 3390 (NH_2), 3280 (NH), 1657 (C=C), 1316 (CH_3), 1094 (C=S). 1H NMR (400 MHz, DMSO-d_6): δ 2.32 (s, 3H, CH3). 5.11 (s, 2H, NH2), 6.78 (t, *J* = 7.6 Hz, 1H, Ar), 6.92 (d, *J* = 7.5 Hz, 2H, Ar+Fu), 7.06 (t, *J* = 7.4 Hz, 1H, Ar), 7.25 (t, J = 7.9 Hz, 2H, Ar), 7.48 (d.d, J = 11.4, 8.0 Hz, 2H, Ar), 7.56 (d, 2H, J = 7.9 Hz, Ar), 8.83 (d, *J* = 11.7 Hz, 1H, =CH), 13.11 (d, *J* = 8.0 Hz, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.33 (CH_3), 104.67 (4-Fu), 115.45 (3-Fu), 116.58, 117.54, 118.87, 119.03, 123.77, 123.89, 125.93, 126.78, 127.78, 130.16, 137.75, 139.89, 147.62 (C=C), 149.31 (C-NH2), 151.68 (5-Fu), 187.52 (C=S). Anal. calcd. for C*18*H*16*N2OS: C: 70.10%; H: 5.23%; N: 9.08%; S: 10.42%; Found: C: 70.64%; H: 5.77%; N: 9.59%; S: 10.82%.

(Z)-3-[((2-aminophenyl)amino)methylidene]-5-(4-chlorophenyl)furan-2(3H)-thione **3g**

Red crystals (toluene), yield 0,25 g (76%), mp 219–221 °C; FTIR, ν, cm^{-1}: 3394 (NH_2), 3282 (NH), 1655 (C=C), 1091 (C=S). 1H NMR (400 MHz, DMSO-d6): δ 5.13 (s, 2H, NH_2), 6.78 (t, *J* = 7.7 Hz, 1H, Ar), 6.92 (d, *J* = 7.9 Hz, 1H, Ar), 7.03–7.08 (m, 2H, Ar+Fu), 7.46–7.52 (m, 3H, Ar), 7.69 (d, *J* = 8.0 Hz, 2H, Ar) 8.87 (d, *J* = 12.0 Hz, 1H, =CH), 13.16 (d, *J* = 12.0 Hz, NH); 13C NMR (100 MHz, DMSO -d6): δ 106.53 (4-Fu), 115.36 (3-Fu), 118.88, 119.20, 125.47, 125.63, 125.84, 128.20, 129.50, 139.92, 148.17 (C=C), 150.24 (5-Fu), 187.70 (C=S). Anal. calcd. for $C_{17}H_{13}N_2OSCl$: C: 62.10%; H: 3.99%; N: 8.52%; S: 9.75%; Cl: 10.78%: Found: C: 62.49%; H: 4.47%; N: 8.95%; S: 10.17%; Cl: 11.10%.

4. Conclusions

Thus, the series of aminomethylidenefuran-2(3*H*)-thiones containing an electron-donor substituent in the aromatic ring of the enamine fragment was expanded using the transamination reaction. It was found that the obtained compounds exist in the form of a *cis*-enamine configuration.

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References

1. Makawana, J.A.; Patel, M.P.; Patel, R.G. Synthesis and in vitro antimicrobial activity of N-arylquinoline derivatives bearing 2-morpholinoquinoline moiety. *Chin. Chem. Lett.* **2012**, *23*, 427–430. https://doi.org/10.1016/j.cclet.2012.01.017.
2. Hundsdörfer, C.; Hemmerling, H.-J.; Götz, C.; Totzke, F.; Bednarski, P.; Le Borgne, M.; Jose, J. Indeno[1,2-b]indole derivatives as a novel class of potent human protein kinase CK2 inhibitors. *Bioorg. Med. Chem.* **2012**, *20*, 2282–2289. https://doi.org/10.1016/j.bmc.2012.02.017.
3. Gonçalves, D.S.; Silva, M.J.V.; Souza, T.F.; Jacomini, A.P.; Back, D.F.; Basso, E.A.; Moura, S. Synthesis of a New Polyfunctionalised Pyrimidine-4-carboxylate and Its Application for the Construction of a Series of Pyrimidine Derivatives. *Synthesis* **2016**, *48*, 3042–3049. https://doi.org/10.1055/s-0035-1561860.
4. Andrade, V.; Mittersteiner, M.; Bonacorso, H.; Frizzo, C.; Martins, M.; Zanatta, N. Regioselective Synthesis of 5-(Trifluoromethyl)[1,2,4]triazolo[1,5-a]pyrimidines from β-Enamino Diketones. *Synthesis* **2019**, *51*, 2311–2317. https://doi.org/10.1055/s-0037-1611765.
5. Ali, M.; Barakat, A.; El-Faham, A.; Al-Majid, A.M.; Yousuf, S.; Ashraf, S.; Albericio, F. Enamine Barbiturates and Thiobarbiturates as a New Class of Bacterial Urease Inhibitors. *Appl. Sci.* **2020**, *10*, 3523–3535. https://doi.org/10.3390/app10103523.
6. Kaping, S.; Kalita, U.; Sunn, M.; Singha, L.O.; Vishwakarma, J.N. A facile, regioselective synthesis of pyrazolo[1, 5-a]pyrimidine analogs in the presence of KHSO4 in aqueous media assisted by ultrasound and their anti-inflammatory and anti-cancer activities. *Monatsh. Chem.* **2016**, *147*, 1257–1276. https://doi.org/10.1007/s00706-015-1638-x.
7. Abu-Bakr, S.M.; Khidre, M.D.; Omar, M.A.; Swelam, S.A.; Awad, H.M. Synthesis of furo[3,2-g]chromones under microwave irradiation and their antitumor activity evaluation. *J. Heterocycl. Chem.* **2019**, *57*, 731–743. https://doi.org/10.1002/jhet.3813.
8. Tikhomolova, A.S.; Grinev, V.S.; Yegorova, A.Y. One-Pot Synthesis, *E*-/*Z*-Equilibrium in Solution of 3-Hetarylaminomethylidenefuran-2(3*H*)-ones and the Way to Selective Synthesis of the *E*-Enamines. *Molecules* **2023**, *28*, 963. https://doi.org/10.3390/molecules28030963.
9. Tikhomolova, A.S.; Mamleeva, Z.V.; Yegorova, A.Y. An efficient synthesis of (*E*)-3-[(dimethylamino)methylidene]furan-2(3*H*)-thiones and transamination reactions thereof. *Chem. Heterocycl. Compd.* **2024**, *60*, 138–142. https://doi.org/10.1007/s10593-024-03309-z.