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Synthesis of new functionalized thiazolidin-4-ones by the condensation of thioureas with dialkyl acetylenedicarboxylates

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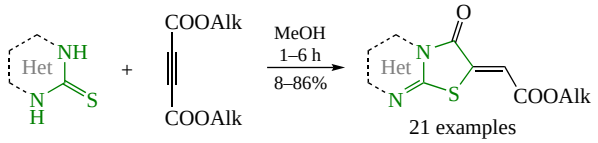
Thiazolidin-4-ones functionalized at the position 5 and their heterocycle-annulated analogues were obtained based on the reaction of thioureas with dialkyl acetylenedicarboxylates. In most cases the reaction proceeds with high selectivity to form 2-iminothiazolidin-4-one-type products.



Keywords: thiazolidin-4-ones, acetylenedicarboxylates, Michael addition, cyclocondensation, thioureas, thiosemicarbazides.

Thiazolidin-4-ones represent a large class of biologically active compounds with a wide range of therapeutic applications and great importance for medicinal chemistry.[1] Among the pharmacologically active thiazolidin-4-ones, special attention is paid to their derivatives functionalized at the position 5, many of which are the main components of currently used antifungal (micosidine),[2] neurotropic (epalrestate),[3] anti-inflammatory (darbufelon),[4] diuretic (ethozoline)[5] and antidiabetic (pioglitazone)[6] drugs. Condensation products of thiazolidin-4-ones with (hetero)aromatic aldehydes or isatins are promising antiviral, antibacterial and anticancer agents.[7]

One of the effective one-step pathways to 5-substituted thiazolidin-4-ones is the condensation of thioamides or thioureas with acetylenedicarboxylic acid esters.[8] The resulting products are interesting not only for studying their biological properties but also for the synthesis of pharmacologically oriented dispirocyclic thiazolidine-pyrrolidine-oxindoles,[9] analogues of the natural alkaloids horsfiline and coerulescine, as well as sulfanyl derivatives of fumaric and aconitic acids.[10]

In the present work, the series of thioureas and their analogues including cyclic structures that can be reacted with acetylenedicarboxylic acid esters has been significantly expanded (Scheme 1). The condensation of thioureas **1a**,**b** with dimethyl or diethyl acetylenedicarboxylates (DMAD or DEAD, respectively) occurred upon boiling the reactants in methanol and led to formation of thiazole ring functionalized at the position 5 rather than thiazine ring as one of the papers reported.[11] The identity of the melting points and ^{1}H NMR spectra data of the compounds described by the authors[11] with the similar data for structures **2a**,**b** indicates the similarity of the products. Analysis of the coupling constants in one-dimensional ^{13}C NMR GATED spectrum of ethyl ester **3b** allows us to unambiguously prove the structure of five-membered products. When unsymmetrical 1-methyl-3-phenylthiourea **1c** was used, the cyclization proceeded selectively at the nitrogen atom linked with the methyl group and led to the only regioisomers **2c** and **3c**.

The regioselectivity of the reactions of 1,4-disubstituted thiosemicarbazides **1d**,**e** and *N*-methylisatin thiosemicarbazone (metisazone) **1f** depended on the substitution situation at the N^4 nitrogen atom of the semicarbazide chain. In the case of the terminal 4-NH$_2$ group in thiosemicarbazone **1f**, the cyclization occurred at the corresponding N^4 nitrogen atom and led exclusively to products **2f** and **3f**. On the contrary, the bulky cyclohexyl substituent in thiosemicarbazide **1d** reduced the nucleophilicity of the corresponding nitrogen atom and directed the intramolecular N-acylation step at the N^2 atom (*cf.* ref. 12). The reaction of 1,4-diphenylthiosemicarbazide **1e** with DMAD proceeded nonselectively and afforded two regioisomeric products **2e** and **2′e** in equal amounts (^{1}H NMR). Compound **2′e** and its isomeric structure **2e** were isolated by fractional crystallization from methanol with the yields of 36 and 8%, respectively.

Heterocyclic compounds **1g**–**m** containing a thiourea moiety reacted with dialkyl acetylenedicarboxylates similarly to acyclic structures and gave thiazolidine-fused bi- or tricyclic heterocyclic systems **2g**–**m** and **3g**,**h**,**m**. In the reaction of pyrimidine-2-thione **1m** with diethyl acetylenedicarboxylate, a by-product **4m** of conjugated addition of two NH groups with two DEAD molecules was formed in addition to the main thiazolo[3,2-*a*]-pyrimidine **3m**.

The structures of the synthesized compounds **2a**–**m**, **3a**–**c**,**f**–**h**,**m** and **4m** were confirmed by IR, ^{1}H and ^{13}C NMR and HRMS spectral data. The structures of regioisomers **2d** and **2′e** were proved using two-dimensional {^{1}H–^{13}C} HMBC NMR experiments (Figure 1). The observed cross-peaks of NH signals with a carbon atom of C^4=O (for **2d**) or C^2=N fragments (for **2′e**) unambiguously prove their structures.

The formation of a five-membered thiazole rather than a six-membered thiazine ring during the cyclocondensation was proven by comparison with the literature data[13] on the spin–spin

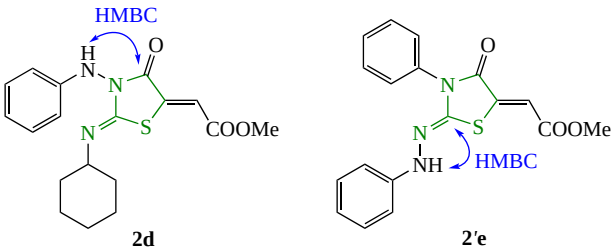
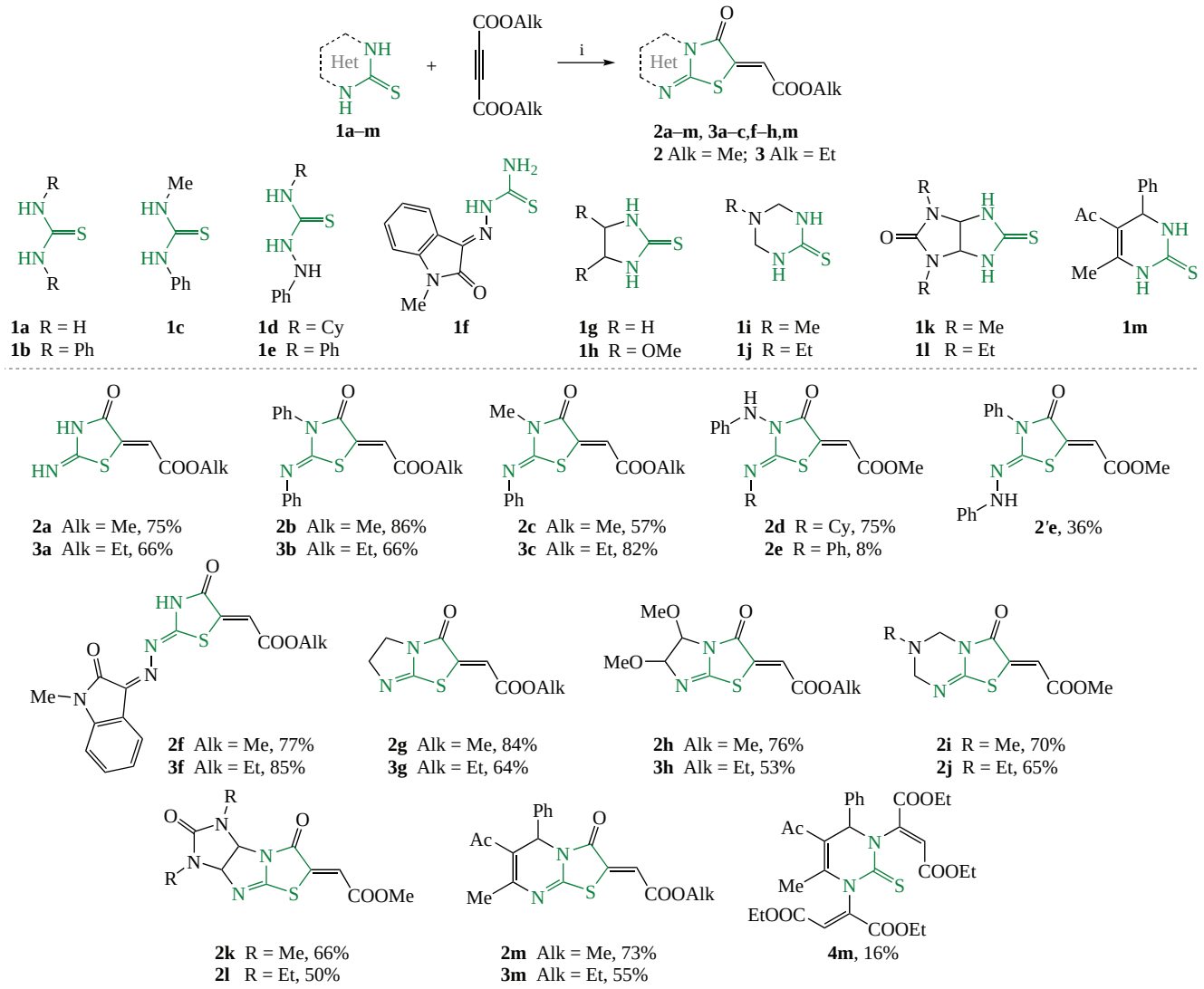


Figure 1 Correlations of the carbon atom of C=O and C=N groups in the {^{1}H–^{13}C} HMBC NMR spectra of compounds **2d** and **2′e**.



Scheme 1 *Reagents and conditions:* i, MeOH, reflux, 1 h (for **2a–c**,**f**,**g**,**k–m** and **3a–c**,**f**,**g**,**m**) or room temperature, 6 h (for **2d**,**e**,**h**,**i**,**j, 2′e** and **3h**).

splitting constants of the signals for carbonyl group carbon atoms (C^4=O) on the vinyl fragment hydrogen atom =CH (Figure 2). In the ^{13}C NMR GATED (see Online Supplementary Materials) spectra of compounds **2d** and **3b**,**g** the signals of the corresponding carbon atoms appear as doublets at 157.8–164.4 ppm with a spin–spin interaction constant $^3J_{CH}$ = 5.3–5.5 Hz, which is characteristic of the mutual *cis*-position of the lactam group and the hydrogen atom relative to the exocyclic C=C bond.

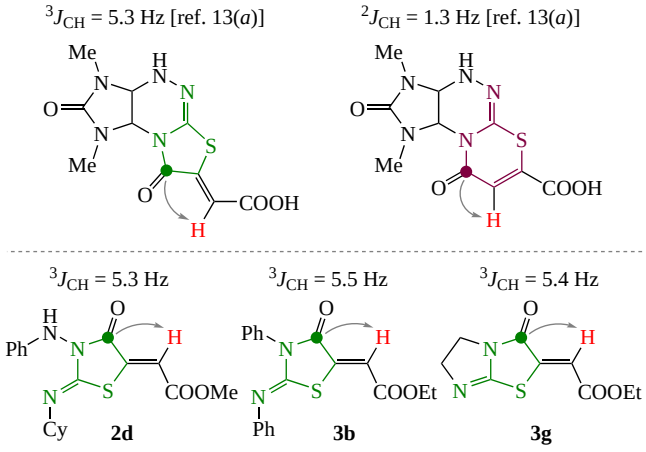


Figure 2 Selected CH-coupling constants $^3J_{CH}$ and $^2J_{CH}$ in thiazole and thiazine rings.

The structures of thiazolidine **2c**, thiazolo[3,2-*a*]pyrimidine **3m** and pyrimidine **4m** were ultimately confirmed by single crystal X-ray diffraction studies (Figure 3).†

† *Crystals* of compounds **2c**, **3m** and **4m** were obtained from a methanol solution.

Crystal data for **2c**. $C_{13}H_{12}N_2O_3S$, M = 276.31, monoclinic, space group $P2_1/c$, 100 K, a = 13.66414(11), b = 12.04434(10) and c = 7.89607(7) Å, α = 90°, β = 103.3809(9)°, γ = 90°, V = 1264.223(19) Å^3, Z = 4, d_{calc} = 1.452 g cm^{-3}, $F(000)$ = 576. Total of 18895 reflections were measured and 2747 independent reflections (R_{int} = 0.0303) were used in a further refinement. R_1 = 0.0293 [from 2694 unique reflections with $I > 2\sigma(I)$] and wR_2 = 0.0753 (from all 2747 unique reflections).

Crystal data for **3m**. $C_{19}H_{18}N_2O_4S$, M = 370.42, monoclinic, space group $P2_1/n$, 100 K, a = 14.84840(11), b = 7.03498(4) and c = 17.76625(13) Å, α = 90°, β = 110.4592(8)°, γ = 90°, V = 1738.77(2) Å^3, Z = 4, d_{calc} = 1.415 g cm^{-3}, $F(000)$ = 776. Total of 24586 reflections were measured and 3772 independent reflections (R_{int} = 0.0235) were used in a further refinement. R_1 = 0.0305 [from 3707 unique reflections with $I > 2\sigma(I)$] and wR_2 = 0.0770 (from all 3772 unique reflections).

Crystal data for **4m**. $C_{29}H_{34}N_2O_9S$, M = 586.64, monoclinic, space group $P2_1/c$, 100 K, a = 9.23607(7), b = 33.7548(2) and c = 10.21901(9) Å, α = 90°, β = 112.7873(9)°, γ = 90°, V = 2937.23(4) Å^3, Z = 4, d_{calc} = 1.327 g cm^{-3}, $F(000)$ = 1240. Total of 37855 reflections were measured and 6391 independent reflections (R_{int} = 0.0270) were used in a further refinement. R_1 = 0.0411 [from 6150 unique reflections with $I > 2\sigma(I)$] and wR_2 = 0.1071 (from all 6391 unique reflections).

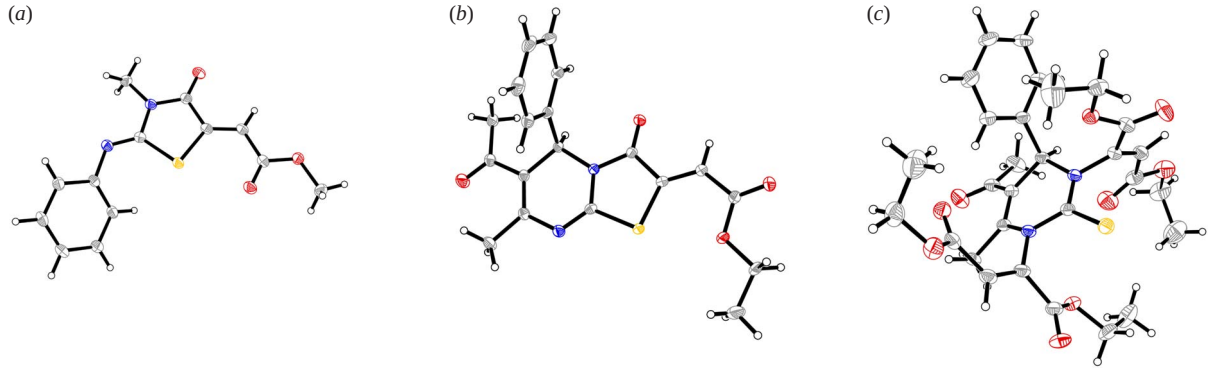


Figure 3 General view of (*a*) compound **2c**, (*b*) compound **3m** and (*c*) compound **4m** in crystals in thermal ellipsoid representation (p = 50%).

In summary, a wide range of different functionalized thiazolidin-4-ones and their heterocycle-annulated analogues have been synthesized based on the condensation of dialkyl acetylenedicarboxylates with thioureas and their derivatives. The reaction proceeds with high selectivity to give a five-membered thiazole ring.

The study was supported by a grant from the Russian Science Foundation (grant no. 23-73-01252, https://rscf.ru/en/project/23-73-01252). Crystal structure determination for compounds **2c**, **3m** and **4m** was performed at the Department of Structural Studies of N. D. Zelinsky Institute of Organic Chemistry, Moscow.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.06.031.

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X-ray diffraction data were collected at 100 K on a four-circle Rigaku Synergy S diffractometer equipped with a HyPix6000HE area-detector (kappa geometry, shutterless ω-scan technique), using monochromatized Cu Kα-radiation. The intensity data were integrated and corrected for absorption and decay by the CrysAlisPro program.[14] The structure was solved by direct methods using SHELXT[15] and refined on F^2 using SHELXL-2018[16] in the OLEX2 program.[17]

CCDC 2343979 (**2c**), 2341187 (**3m**) and 2343094 (**4m**) contain the supplementary crystallographic data for this paper. The data can obtained free of charge from The Cambridge Crystallographic Data Center *via* http://www.ccdc.cam.ac.uk.

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