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# Sulfonyl derivatives of 1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazines in reactions with acyl/alkyl halides

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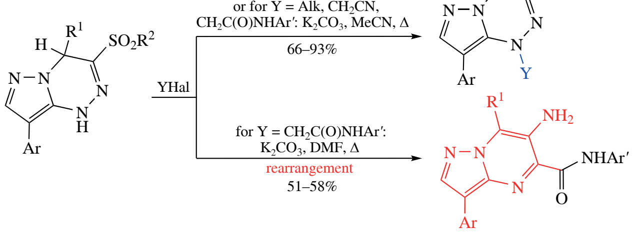
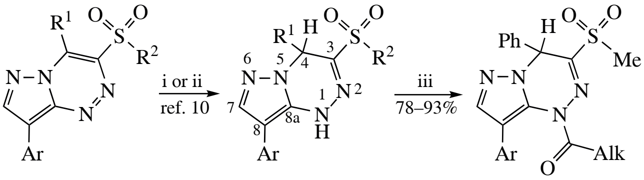
**The acylation reaction of 3-sulfonyl-1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazines with acid chlorides on heating in the corresponding carboxylic acids gives the acylated derivatives at the N$^1$ atom of the *as*-dihydrotriazine ring. The analogous reactions with various alkyl halides in the $K_2CO_3$–MeCN system proceed similarly. When the alkylation with chloroacetanilides is performed on heating in $K_2CO_3$–DMF, a cascade rearrangement is initiated with the loss of the sulfonyl group and recyclization into 6-aminopyrazolo[1,5-*a*]pyrimidine-5-carboxamides.**



*Keywords*: pyrazolo[5,1-*c*][1,2,4]triazines, pyrazolo[1,5-*a*]pyrimidines, sulfones, substitution, rearrangement, cascade reactions, acylation, alkylation, carboxamides, X-ray diffraction analysis.

Pyrazolo[5,1-*c*][1,2,4]triazines are promising due to the possibility of their pharmacological use as antiviral,[1] antineoplastic,[2] antifungal,[3] antidiabetic[4] and antibacterial[5] agents. Partially hydrogenated pyrazolo[5,1-*c*][1,2,4]triazines also exhibit tuberculostatic[6] activity. Thus, the combination of pyrazolo[5,1-*c*][1,2,4]triazine system and its partially hydrogenated analogs with different pharmacophoric groups allows one to anticipate a certain pharmacological effect in new derivatives. In this regard, sulfone derivatives of the considered systems are of interest. The sulfonyl group is pharmacophoric and is found in representatives of many classes of biologically active compounds.[7] Despite the high synthetic and pharmacological potential, sulfonyl derivatives of pyrazolo-*as*-triazines are still poorly studied.[8–11] It was earlier[10] found that 3-mesyl- and 3-tosylpyrazolo[5,1-*c*][1,2,4]triazines **1a–c** participated in reduction reactions with the formation of the corresponding sulfonyl derivatives of 1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazines **2a–c** (Scheme 1). The presence in the structure of the latter of several reaction centers should allow one to carry out their multiple functionalization while the presence of easily leaving mesyl and tosyl groups can initiate new cascade transformations.



**1a–c** **2a–c** **3a–c** (from **2a**,**b**)

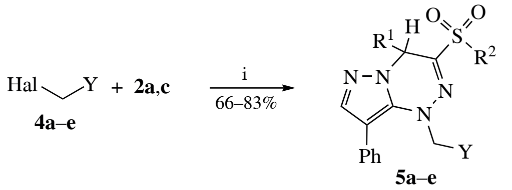
**1a**, **2a** Ar = R$^1$ = Ph, R$^2$ = Me
**1b**, **2b** Ar = 4-ClC$_6$H$_4$, R$^1$ = Ph, R$^2$ = Me
**1c**, **2c** Ar = Ph, R$^1$ = Me, R$^2$ = 4-MeC$_6$H$_4$
**3a** Ar = Ph, Alk = Me
**3b** Ar = 4-ClC$_6$H$_4$, Alk = Me
**3c** Ar = 4-ClC$_6$H$_4$, Alk = Et

**Scheme 1** *Reagents and conditions*: i, thiourea dioxide; ii, NaBH$_4$, NaOH (0.1 M aq.), EtOH, 60–80 °C; iii, AlkC(O)Cl, AlkCO$_2$H, Δ.

The aim of this work was to study the chemical properties of the obtained sulfonyl derivatives **2a–c** and to modify them. In the continuing research[9–11] we studied the reactions of 3-mesyl- and 3-tosyl-1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazines with some acyl and alkyl halides. When compounds **2a**,**b** were heated with acetyl or propionyl chlorides in the medium of the corresponding carboxylic acids, *N*-acyl derivatives **3a–c** were obtained in good yields (see Scheme 1). Carboxylic acids were chosen as the reaction medium in order to: (1) provide acid catalysis; (2) use them as good solvents for initial substances; (3) reduce the probability of side reactions.

In the $^1$H NMR spectra of the products, singlets for NH protons at ~12 ppm were absent and signals for acyl groups were observed. The $^{13}$C NMR spectra contained the signals of amide carbon atoms in the range of ~167–170 ppm. Strong absorption bands of C=O groups at 1728–1741 cm$^{-1}$ appeared in the IR spectra, while the bands of cyclic NH groups (3200 cm$^{-1}$) disappeared.

When compounds **2a**,**c** were heated with alkyl halides **4a**,**b**, chloroacetonitrile **4c** and chloroacetamides **4d–e** in acetonitrile in the presence of potassium carbonate, the corresponding *N*-alkyl derivatives of dihydropyrazolotriazines **5a–e** were formed in good yields (Scheme 2). In the IR spectra of all these derivatives intense characteristic absorption bands of sulfonyl groups were recorded in two frequency ranges (1132–1153 and 1309–1317 cm$^{-1}$). Wide absorption band (~2364 cm$^{-1}$) in the IR spectrum of product **5c** indicates the presence of a nitrile group. $^1$H and $^{13}$C NMR spectra of compound **5a** contain the signals for $CH_3$ group, while signals for $CH_2$ groups at $\delta_H \approx 4.6$ and



**4a–e**

**5a–e**

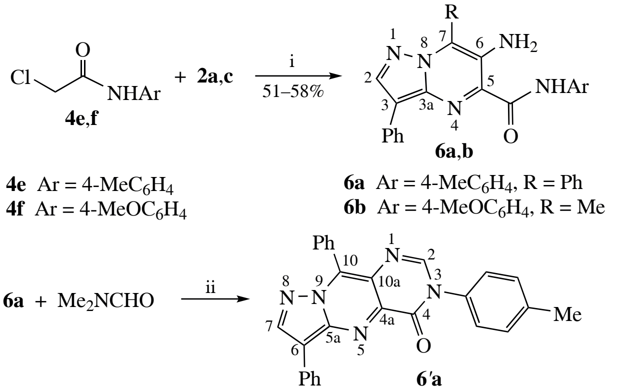
**4a** Y = H, Hal = I
**4b** Y = Me, Hal = Br
**4c** Y = CN, Hal = Cl
**4d** Y = C(O)NHPh, Hal = Cl
**4e** Y = C(O)NH(C$_6$H$_4$Me-4), Hal = Cl

**5a** Y = H, R$^1$ = Ph, R$^2$ = Me
**5b** Y = R$^2$ = Me, R$^1$ = Ph
**5c** Y = CN, R$^1$ = Me, R$^2$ = 4-MeC$_6$H$_4$
**5d** Y = C(O)NHPh, R$^1$ = Ph, R$^2$ = Me
**5e** Y = C(O)NH(C$_6$H$_4$Me-4), R$^1$ = Ph, R$^2$ = Me

**Scheme 2** *Reagents and conditions*: i, K$_2$CO$_3$, MeCN, 80 °C, 3–4 h.

$\delta_C \approx 43$–56 were revealed in the spectra of compounds **5b–e**. The presence of a stereogenic carbon atom (C$^4$) in the molecules of the acyl and alkyl derivatives of dihydropyrazolotriazines **3a–c** and **5a–e** determines the possibility of their existence in the form of *R*/*S*-enantiomers. In the $^1$H NMR spectra of compounds **3a–c** and **5a**,**b**,**d**,**e** (Ph substituent at C$^4$H), the corresponding C$^4$*H* protons resonate as singlets at $\delta_H$ = 6.56–6.68, whereas for compound **5c** (R$^1$ = Me), the C$^4$*H* proton expectedly appears as a quartet at $\delta_H$ 5.66 ($J \approx 6.5$ Hz). In comparison, N$^1$-unsubstituted dihydropyrazolotriazines **2a–c** show similar spectral characteristics ($\delta_H \approx 6.5$–6.6, R$^2$ = Ph and $\delta_H \approx 5.6$, $J \approx 6.5$ Hz, R$^1$ = Me), indicating the same configuration of their asymmetric centers (*cf*. ref. 10). It is interesting to note that in $^1$H and $^{13}$C NMR spectra of compound **5a**, the following signals were doubled: signals of protons at the C$^4$ atom ($\delta_H$ = 5.75 and 6.56 in a ratio of ~1 : 1) and peaks of carbon nuclei C$^4$ ($\delta_C$ = 54.78 and 56.90). At the same time, double sets of signals were not observed in the NMR spectra of compounds **3a–c** and **5b–e**. It is known that the appearance of individual signals of enantiomers in NMR spectra may be associated with the phenomenon of self-induced diastereomeric anisochronism (SIDA).[12] Probably, the presence of a relatively bulky methyl substituent at the N$^1$ atom of the dihydrotriazine ring in compound **5a**, unlike compounds **3a–c** and **5b–e**, sterically provides the possibility for the formation of associates between (*S*)- and (*R*)-enantiomers in DMSO-*d*$_6$ solution due to intermolecular S=O···H–C and weak π–π stacking interactions. In addition, a low melting point (78–80 °C), not typical for other representatives of similar systems, may indicate the existence of compound **5a** as a racemic mixture.

The reactions of dihydropyrazolotriazines with compounds **4e**,**f** in a high-boiling aprotic solvent such as DMF led to a change in the reaction pathway and to the formation of 6-aminopyrazolo[1,5-*a*]pyrimidine-5-carboxamides **6a**,**b** (Scheme 3), what has been proven by HPLC-MS and $^1$H and $^{13}$C NMR spectroscopy. In $^1$H NMR spectra of the compounds obtained, the proton signals for the methanesulfonyl group disappeared, but singlets of two protons appeared in the $\delta_H$ range of ~5.56–5.99. The positions of the signals of amide protons ($\delta_H \approx 10.5$) in the products differed from those for the H-atoms bound to the endocyclic nitrogen atom of the starting reagents[10] ($\delta_H \approx 11.9$). In the $^{13}$C NMR spectra, signals of the amide carbon atom appeared at $\delta_C \approx 164$. The IR spectra of the obtained compounds also lack characteristic absorption bands of sulfonyl groups, but a strong narrow absorption band of C=O amide groups was observed at ~1675 cm$^{-1}$. For the confirmation of the structure of the compounds obtained and assigning signals in one-dimensional NMR spectra, two-dimensional correlation experiments (NOESY, COSY, HSQC, HMBC) were carried out for compounds **5c** and **6a**. Correlations in two-dimensional spectra of these compounds are presented in Online Supplementary Materials, Tables S1 and S2, respectively.



**4e**,**f**

**6a**,**b**

**4e** Ar = 4-MeC$_6$H$_4$
**4f** Ar = 4-MeOC$_6$H$_4$

**6a** Ar = 4-MeC$_6$H$_4$, R = Ph
**6b** Ar = 4-MeOC$_6$H$_4$, R = Me

**6′a**

**Scheme 3** *Reagents and conditions*: i, K$_2$CO$_3$, DMF, 150 °C, 15–20 min; ii, DMF, 150 °C, 5–7 min.

To more strictly prove the structures of **6a**,**b**, it was decided to grow a single crystal of one of the compounds for X-ray diffraction study. Both substances turned out to be poorly soluble, so high-boiling polar solvents (DMF, DMA, DMSO) were tested. It was possible to obtain a single crystal only from a solution of DMF for compound **6a**. It turned out that in the course of the dissolution on heating of compound **6a** in DMF, a further transformation occurred with the production of 6,10-diphenyl-3-(*p*-tolyl)pyrazolo-[1,5-*a*]pyrimido[5,4-*d*]-pyrimidin-4(3*H*)-one **6′a** (Figure 1).† Apparently, this new heterocyclic system was formed through the intermolecular heterocyclization of amino and amide groups of compound **6a** with one molecule of DMF acting as a C$_1$ synthon[13] to result in a 2-positioned carbon atom in **6′a** (see Scheme 3).

To understand the mechanistic pathway to products **6a**,**b** (see Scheme 3), we analyzed in time the reaction mixtures of

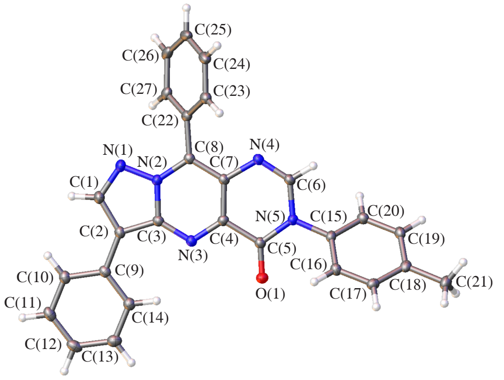


**Figure 1** General view of compound **6′a**. Non-hydrogen atoms are shown as thermal ellipsoids at 50% probability level. Atom numbering does not correspond to the systematic one.

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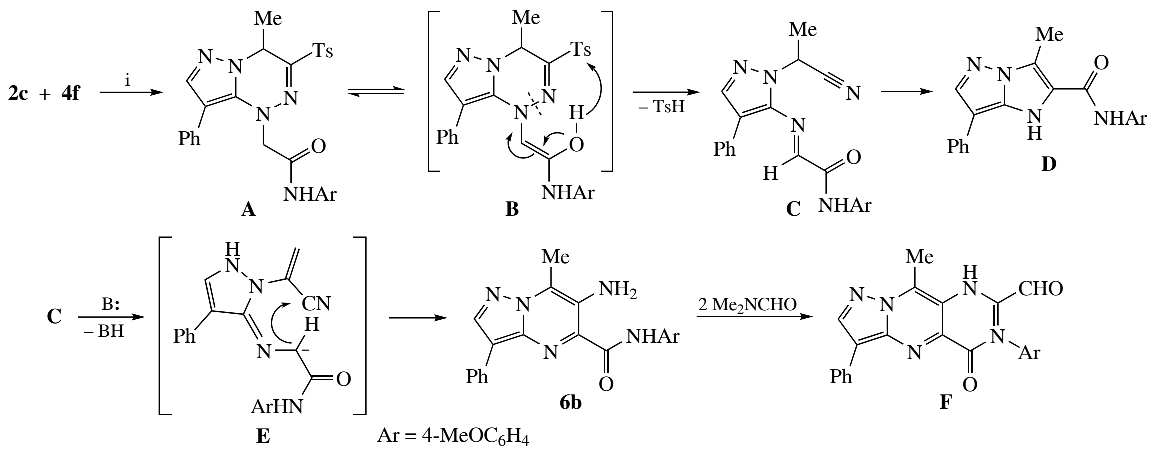
† *Crystal data for* **6′a**. C$_{27}$H$_{19}$N$_5$O, $M$ = 429.47, monoclinic, space group $P2_1/c$, at 120 K, $a$ = 7.0433(3), $b$ = 16.0608(7) and $c$ = 18.1653(8) Å, $\beta$ = 95.8910(10)°, $V$ = 2044.02(15) Å$^3$, $Z$ = 4 ($Z'$ = 1), $d_{calc}$ = 1.396 g cm$^{-3}$, $\mu$(MoKα) = 0.89 cm$^{-1}$, $F$(000) = 896. Intensities of 38909 reflections were measured with a Bruker APEXII DUO CCD diffractometer [$\lambda$(MoKα = 0.71073 Å, ω-scans, $2\theta < 56°$], and 4924 independent reflections were used in the further refinement. Using Olex2, the structure was solved with the ShelXT structure solution program using Intrinsic Phasing and refined with the XL refinement package using Least-Squares minimization. Positions of hydrogen atoms were calculated, and they were refined in the isotropic approximation within the riding model. The refinement converged to $wR_2$ = 0.1083 and GOF = 1.035 for all the independent reflections [$R_1$ = 0.0411 was calculated against $F$ for 4087 observed reflections with $I > 2\sigma(I)$].

CCDC 2142098 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* https://www.ccdc.cam.ac.uk.



**Scheme 4** *Reagents and conditions*: i, DMF, $K_2CO_3$, Δ.

compounds **2c** and **4f** in $K_2CO_3$/DMF using HPLC/MS in combination with UV detection. The signals were interpreted on the basis of pre-calculated masses in the form of molecular ions with $[M+H]^+$ and referred to possible initial, intermediate and formed substances (Scheme 4, also see Online Supplementary Materials, Table S3 and Figures S2–S5). When the substrates were mixed at room temperature, the product of *N*-alkylation of dihydropyrazolotriazine (intermediate **A**) began to appear (see Figure S2). Further heating for 5 min (Figure S3) with raising the temperature to 80 °C led to an increase in the concentration of intermediate **A** and a decrease in the concentration of the initial reagents without the appearance of other products. However, when the mixture was heated to 150 °C (10 min after the start of the reaction, Figure S4), new peaks were observed on the chromatogram which could be attributed to the ring opening product of *as*-triazine (intermediate **C**) and the rearrangement product, substituted pyrazolo[1,5-*a*]pyrimidine **6b** (probably *via* an unstable intermediate **E**). Further heating of the reaction mixture at 150 °C (20 min from the beginning of the reaction, Figure S5) made it possible to record the maximum peak of the rearrangement product **6b** and to reveal side processes with the formation of the cycle contraction product, imidazo[1,2-*b*]pyrazole derivative **D**, and the product of double formylation of pyrazolopyrimidine **6b** with DMF (compound **F**). Heating the reaction mixture for more than 20 min resulted in a significant increase in the number of by-products that were difficult to identify. Thus, the predominant reaction pathway is the cascade process during which the 1,4-dihydrotriazine ring opens under the action of a base to form a key nitrile intermediate **C** which would subsequently undergo the Thorpe–Ziegler-type cyclization[14] with pyrimidine ring closure (see Scheme 4). The prolonged heating of the reaction mixture is undesirable since it leads to the formation of formylation products.

In summary, the reactions of 3-sulfonyl derivatives of 1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazines with carboxylic acid chlorides in the medium of the corresponding acids as well as with some alkyl chlorides upon heating in system $K_2CO_3$–MeCN proceed regioselectively at the $N^1$ atom of the partially hydrogenated *as*-triazine. The reactions with chloroacetamides in system $K_2CO_3$–DMF lead to a cascade process proceeding through the opening of the dihydrotriazine ring and subsequent recyclization with the formation of 6-aminopyrazolo[5,1-*a*]pyrimidine-5-carboxamide derivatives.

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*Online Supplementary Materials*

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7846.

## References

1 I. M. Sapozhnikova, E. N. Ulomsky, V. L. Rusinov, O. N. Chupakhin, A. V. Stepanov, T. N. Savateeva-Lyubimova and K. V. Sivak, *Chem. Heterocycl. Compd.*, 2021, **57**, 467; https://doi.org/10.1007/s10593-021-02925-3.

2 D. M. Berger, M. D. Dutia, D. W. Hopper and N. Torres, *Patent WO 2009039387 A1*, 2009.

3 S. A. Al-Trawneh, S. A. Al-Dawdieh, N. S. Abutaleb, A. H. Tarawneh, E. A. Salama, M. M. El-Abadelah and M. N. Seleem, *Chem. Pap.*, 2020, **74**, 1241; https://doi.org/10.1007/s11696-019-00974-9.

4 V. L. Rusinov, I. M. Sapozhnikova, A. M. Bliznik, O. N. Chupakhin, V. N. Charushin, A. A. Spasov, P. M. Vassiliev, V. A. Kuznetsova, A. I. Rashchenko and D. A. Babkov, *Arch. Pharm.*, 2017, **350**, 1600361; https://doi.org/10.1002/ardp.201600361.

5 W. M. Al-Adiwish, M. A. S. Abubakr and N. M. Alarafi, *Cell Biol.*, 2017, **5**, 45; https://doi.org/10.11648/j.cb.20170505.11.

6 E. V. Shchegol'kov, O. G. Khudina, A. E. Ivanova, Ya. V. Burgart, E. V. Sadchikova, M. A. Kravchenko and V. I. Saloutin, *Pharm. Chem. J.*, 2014, **48**, 383; https://doi.org/10.1007/s11094-014-1115-6.

7 X. Chen, S. Hussain, S. Parveen, S. Zhang, Y. Yang and C. Zhu, *Curr. Med. Chem.*, 2012, **19**, 3578; https://doi.org/10.2174/092986712801323225.

8 A. O. Abdelhamid, H. M. Hassaneen and A. S. Shawali, *J. Heterocycl. Chem.*, 1985, **22**, 453; https://doi.org/10.1002/jhet.5570220249.

9 I. V. Ledenyova, P. A. Kartavtsev, Kh. S. Shikhaliev and A. Yu. Egorova, *Russ. J. Org. Chem.*, 2016, **52**, 1316; https://doi.org/10.1134/S1070428016090116.

10 I. V. Ledenyova, P. A. Kartavtsev, Kh. S. Shikhaliev and A. Yu. Egorova, *Chem. Heterocycl. Compd.*, 2017, **53**, 1128; https://doi.org/10.1007/s10593-017-2183-9.

11 I. V. Ledenyova, P. A. Kartavtsev, N. V. Stolpovskaya and Kh. S. Shikhaliev, *Russ. Chem. Bull.*, 2024, **73**, 1342; https://doi.org/10.1007/s11172-024-4252-4.

12 A. Baumann, A.Wzorek, V. A. Soloshonok, K. D. Klika and A. K. Miller, *Symmetry*, 2020, **12**, 1106; https://doi.org/10.3390/sym12071106.

13 M. M. Heravi, M. Ghavidel and L. Mohammadkhani, *RSC Adv.*, 2018, **8**, 27832; https://doi.org/10.1039/C8RA04985H.

14 L. Amiri-Zirtol, Z. Karimi, F. Azodzadegan and P. Gholamzadeh, in *Advances in Heterocyclic Chemistry*, eds. E. F. V. Scriven and C. A. Ramsden, Academic Press, 2025, vol. 145, pp. 69–96; https://doi.org/10.1016/bs.aihch.2024.10.002.

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