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Regioselective synthesis of novel 4-aryl-2-ethylthio-7-methyl pyrazolo[1,5-*a*]-[1,3,5]-triazines

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Abstract—Pyrazolo[1,5-*a*]-[1,3,5]-triazines **6a–d** were obtained by an efficient one-step reaction from *S*,*S*-diethyl aroyliminodithiocarbonates **4a–d** and 5-amino-3-methylpyrazole **5** or by an alternative two-step reaction from **5** and aroyl isothiocyanates **8a–d** to give initially the thiourea derivatives **9a–d**, which after S-ethylation and cyclization afforded compounds **6a–d**. The intermediate **7a** isolated from reaction between **4a** and **5** permitted us to establish the orientation.

1. Introduction

Derivatives of the ring system pyrazolo[1,5-*a*]-[1,3,5]-triazine are of great interest as purine analogues.[1,2] Additionally, these compounds are active agents to inhibit bronchial inflammation (**1**, Fig. 1)[1d] and are useful in the treatment and prevention of central nervous system disorders,[1e] such as psychosis, schizophrenia, depressions, memory disorders, Parkinson's disease, Alzheimer's disease and Huntington's chorea (**2**, Fig. 1). Other pyrazolotriazines have been used in the treatment of metabolic and peripheral disorders[1f] and recently, compound **3** (Fig. 1) was reported as a powerful Corticotrophin Releasing Factor type 1 (CFR_1) receptor antagonist.[1g] CFR_1 plays an important role in modulating the endocrinal, autonomic, behavioural and immune responses to stress.[1h]

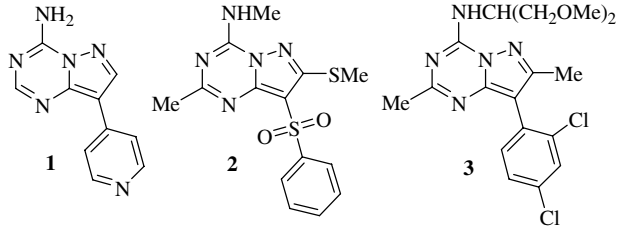

Figure 1.

The most common strategy for preparing pyrazolo[1,5-*a*]-[1,3,5]-triazines is the reaction between 5-aminopyrazoles and an appropriate biselectrophilic reagent.[1c,2] *S*,*S*-Dialkyl aroyliminodithiocarbonates[3] and aroyl isothiocyanates[3a,4] are good bielectrophiles that have been widely used in the synthesis of many heterocyclic compounds, such as monocyclic 1,3,5-triazines,[3c,4c] by reaction with amidines or guanidines. To the best of our knowledge, their use have not been reported for the preparation of pyrazolo[1,5-*a*]-[1,3,5]-triazines. We describe here the interaction of *S*,*S*-diethyl aroyliminodithiocarbonates **4a–d** and aroyl isothiocyanates **8a–d** with 5-amino-3-methylpyrazole **5** as an efficient and versatile method to obtain novel 4-aryl-2-ethylthio-7-methylpyrazolo[1,5-*a*]-[1,3,5]-triazines **6a–d**, interesting compounds in view of their potential biological activity.[1,2,5]

2. Results and discussion

We have devised an efficient one-step procedure for the synthesis of new pyrazolo[1,5-*a*]-[1,3,5]-triazines **6a–d**,[6]

Keywords: 5-Amino-3-methylpyrazole; *S*,*S*-Diethyl aroyliminodithiocarbonates; Aroyl isothiocyanates; Pyrazolo[1,5-*a*]-[1,3,5]-triazines; Thioureas; Isothioureas.

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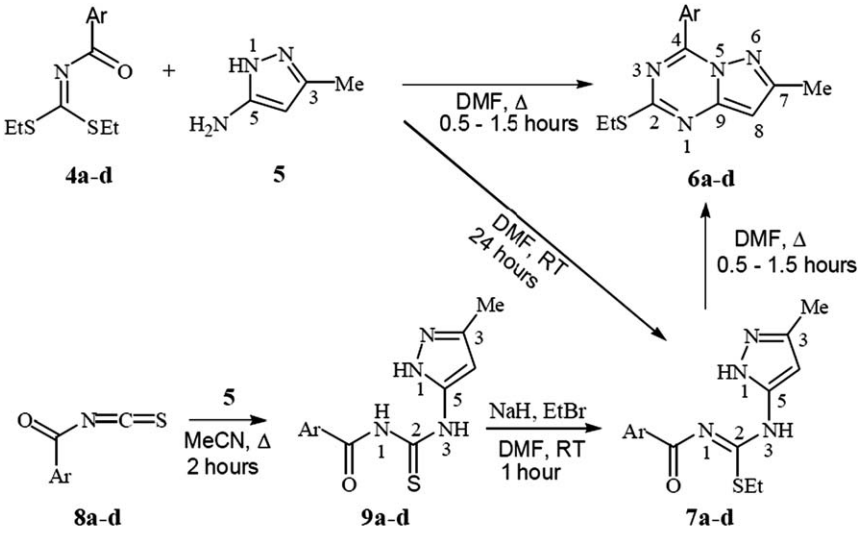

Comp.	Ar	mp., °C	Yield, %[a]
6a	C_6H_5	94	90/87
6b	4-$CH_3C_6H_4$	112	74/80
6c	4-ClC_6H_4	104	93/90
6d	4-$O_2NC_6H_4$	120	61/75
9a	C_6H_5	209	95
9b	4-$CH_3C_6H_4$	220	89
9c	4-ClC_6H_4	208	96
9d	4-$O_2NC_6H_4$	210	70

[a]Yield following method A/method B, for compounds **6a-d**[6]

Scheme 1.

from *S*,*S*-diethyl aroyliminodithiocarbonates[3] **4a–d** and 5-aminopyrazole **5**. Thus, equimolar amounts of **4a–d** and **5** were refluxed in dimethylformamide (DMF) to give compounds **6a–d** in a short time and with good yields (Scheme 1).

The regioselectivity and the mechanism path of reaction between **4** and **5** were established after isolation of intermediate **7a**,[7] which was prepared by reaction between **4a** and **5** in DMF at room temperature for 24 h. Compound **7a** was refluxed in DMF for 1 h to yield the expected compound **6a** (Scheme 1).

Hence, the formation of **6a** is assumed to proceed through an initial addition–elimination: first, the C=N double bond of compound **4a** suffers an addition from exocyclic nitrogen at pyrazole **5**, which after subsequent ethanethiol elimination, affords the adduct **7a**, which after further intramolecular cyclocondensation between endocyclic NH and carbonyl group, leads to pyrazolotriazine **6a**.

In order to provide further evidence to support the above assumption, we have devised an alternate two-step reaction to prepare compounds **6a–d**. In the first step, 5-aminopyrazole **5** and aroyl isothiocyanates[3a,4] **8a–d** were refluxed in acetonitrile for 2 h to give thiourea derivatives **9a–d**[8] (Scheme 1). In the second step, compounds **9a–d** were treated with ethyl bromide in the presence of sodium hydride in DMF at room temperature for 1 h to render the intermediate isothiourea **7a–d**, which although was impossible to isolate; their formation was confirmed by other means, as described below. So, we skipped this latter step to obtain **6**, and so proved our previous assumption. To confirm the formation of intermediate **7a–d**, we repeated the S-ethylation reaction and, when TLC monitoring indicated the formation of compounds **7a–d**, the reaction mixture was refluxed for 0.5–1.5 h yielding the desired compounds **6a–d**[6] (Scheme 1).

The structures of all new compounds were established by spectroscopic methods (IR, NMR ^1H and ^{13}C), mass spectrometry. Additionally, the isolation of single crystals of compounds **6b** and **6d** allowed us to corroborate unambiguously the proposed structure by X-ray diffraction analysis.[9]

3. Conclusion

The two reported routes are simple and practical methods for the preparation of novel 4-aryl-2-ethylthio-7-methylpyrazolo[1,5-*a*]-[1,3,5]-triazines in a short reaction time and with good yields, under mild conditions. Our findings are an important contribution to confirm the selectivity and the mechanism of this kind of reactions.

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6. Preparation of 4-aryl-2-ethylthio-7-methylpyrazolo[1,5-*a*]-1,3,5-triazines (**6a**–**d**). *Method A*. A solution of appropriate *S*,*S*-diethyl aroyliminodithiocarbonate **4a**–**d** (0.003 mol) and 5-amino-3-methylpyrazole **5** (0.003 mol) in dimethylformamide (2 mL) was refluxed for 0.5–1.5 h. The solid products were precipitated by the addition of cold water to the reaction mixture, collected by filtration and purified by column chromatography on silica gel, using a mixture of hexanes/ethyl acetate (4:1) as eluent. *Method B*. A solution of ethyl bromide (0.002 mol) was added dropwise to a suspension of the corresponding thiourea **9a**–**d** (0.002 mol) and sodium hydride (0.002 mol) in dimethylformamide (2 mL). The reaction mixture was then stirred at room temperature for 1 h and refluxed for 0.5–1.5 h. After the dilution of the mixture with cold water, precipitated crystals were filtered and recrystallized from ethanol. Data for **6a**. Yellow solid, mp 94 °C (90%). ^{1}H NMR (400 MHz, DMSO): δ 1.36 (t, 3H, CH_3), 2.43 (s, 3H, 7-CH_3), 3.16 (*c*, 2H, CH_2), 6.41 (s, 1H, 8-H), 7.62 (t, 2H, H*m*), 7.70 (t, 1H, H*p*), 8.57 (d, 2H, H*o*). ^{13}C NMR (DMSO): δ 14.3 (CH_3), 14.6 (7-CH_3), 24.8 (CH_2), 94.2 (C-8), 128.4 (C*m*), 129.6 (C*i*), 130.9 (C*o*), 133.1 (C*p*), 150.8 (C-9), 152.0 (C-4), 157.4 (C-7), 165.0 (C-2). EIMS: *m*/*z*: 270 (M^+, 100), 255 (24), 242 (10), 237 (57), 210 (12), 139 (43%), 105 (33), 77 (18), 51 (20), 39 (16). HMRS (EI): $C_{14}H_{14}N_4S$: requires 270.0944; found: 270.0939.
7. Preparation of 1-benzoyl-2-ethyl-3-(3-methylpyrazol-5-yl)-isothiourea (**7a**). A solution of **4a** (0.003 mol) and **5** (0.003 mol) in dimethylformamide (2 ml) was stirred at room temperature for 24 h. The solid product was precipitated by the addition of cold water to the reaction mixture, collected by filtration and purified by column chromatography on silica gel, using a mixture of hexanes/ethyl acetate (4:1) as eluent. Colourless crystals, mp 123 °C (76%). ^{1}H NMR (400 MHz, DMSO): δ 1.28 (t, 3H, CH_3), 2.23 (s, 3H, 3-CH_3), 3.00 (*c*, 2H, CH_2), 5.92 (s, 1H, 4-H), 7.58 (t, 2H, H*m*), 7.68 (t, 1H, H*p*), 7.96 (d, 2H, H*o*), 12.58 (s, 1H, 1-NH), 13.26 (s, 1H, 3-NH). ^{13}C NMR (DMSO): δ 10.5 (3-CH_3), 13.6 (CH_3), 24.3 (CH_2), 101.3 (C-4), 127.4 (C*m*), 128.2 (C*i*), 129.0 (C*o*), 132.9 (C*p*), 139.3 (C-3), 151.1 (C-5), 155.7 (C-2), 163.9 (C=O). EIMS: *m*/*z*: 288 (M^+, 5), 271 (5), 255 (6), 227 (6), 142 (12), 105 (100), 77 (54), 51 (17), 39 (8). HMRS (EI): $C_{14}H_{16}N_4OS$: requires 288.1049; found: 288.1045.
8. Preparation of 1-aroyl-3-(3-methylpyrazol-5-yl)-thioureas (**9a**–**d**). A solution of compound **5** (0.019 mol) in acetonitrile (10 mL) was added dropwise to a suspension of proper aroyl isothiocyanates **8a**–**d** (0.019 mol) (prepared in situ from corresponding aroyl chloride and potassium thiocyanate) in acetonitrile (20 mL) and then the mixture was refluxed for 2 h. After cooling overnight, the resulting white solid was filtered, washed with ethanol and recrystallized from ethanol. Data for **9a**. White crystals, mp 209 °C (95%). ^{1}H NMR (400 MHz, DMSO): δ 2.25 (s, 3H, 3-CH_3), 6.87 (s, 1H, 4-H), 7.52 (t, 2H, H*m*), 7.64 (t, 1H, H*p*), 7.96 (d, 2H, H*o*), 11.52 (s, 1H, exocyclic 1-NH), 12.45 (s, 1H, endocyclic 1-NH), 13.09 (s, 1H, 3-NH). ^{13}C NMR (DMSO): δ 10.7 (3-CH_3), 97.4 (C-4), 128.4 (C*m*), 128.7 (C*o*), 132.1 (C*i*), 133.1 (C*p*), 138.4 (C-3), 146.9 (C-5), 168.7 (C=O), 176.5 (C=S). EIMS: *m*/*z*: 260 (M^+, 30), 139 (37), 105 (100), 97 (25), 77 (94), 51 (31), 39 (13). HMRS (EI): $C_{12}H_{12}N_4OS$: requires 260.0732; found: 260.0732.
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