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NOTE

New Route for the Synthesis of Pyrimido[4',5':4,5]thiazolo[3,2-a]benzimidazol-4(3*H*)-ones

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A new route for the synthesis of 2-arylpyrimido[4',5':4,5]thiazolo[3,2-a]benzimidazol-4(3*H*)ones has been developed through heterocyclization of 3-aminothiazolo[3,2-a]benzimidazol-2-carboxamide with aromatic aldehydes in boiling glacial acetic acid followed by air oxidation.

Key Words: Pyrimido[4',5':4,5]thiazolo[3,2-a]benzimidazol-4(3*H*)-ones, 3-Aminothiazolo[3,2-a]benzimidazol-2-carboxamide, Aromatic aldehydes, Heterocyclization.

Pyrimido[4',5':4,5]thiazolo[3,2-a]benzimidazoles as potential biologically active heterocycles have been the subject of recent studies[1-3]. The synthetic routes to these compounds are limited and mainly involve cyclocondensation of 3-aminothiazolo-[3,2-a]benzimidazol-2-carbonitrile and 3-aminothiazolo[3,2-a]benzimidazol-2-carboxamide with electrophilic reagents such as formamide, acetic anhydride, orthoesters in combination with amines and aroyl halides[3,4]. Derivatives of these compounds have also been prepared through nucleophilic substitution reactions of the chloro and thio derivatives with different nucleophilic reagents like hydrazine, thiourea and amines[1]. To the best of our knowledge, heterocyclization of 3-amino-thiazolo[3,2-a]benzimidazol-2-carboxamide (**1**) with aromatic aldehydes for the synthesis of 2-arylpyrimido[4',5':4,5]thiazolo[3,2-a]benzimidazoles (**3a-f**) has not been reported in the literature.

In connection with our interest in the synthesis of heterocyclic compounds with potential biological activities[5-16] we report herein a new route for the synthesis of 2-arylpyrimido[4',5':4,5]thiazolo[3,2-a]benzimidazol-4(3*H*)-ones (**3a-f**) through heterocyclization of 3-aminothiazolo[3,2-a]benzimidazol-2-carboxamide (**1**) with aromatic aldehydes in boiling glacial acetic acid followed by air oxidation (**Scheme-I**).

Melting points were recorded on an electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrophotometer as KBr disks. The ^{1}H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. The mass spectra were scanned on a Varian Mat CH-7 instrument at 70 eV.

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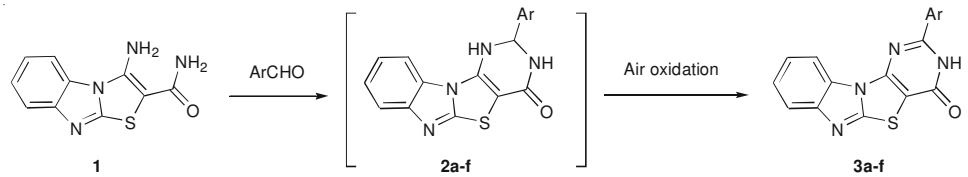

1 **2a-f** **3a-f**

a: Ar = Ph, **b**: Ar = 3-ClC_6H_4, **c**: Ar = 4-ClC_6H_4, **d**: Ar = 3-$NO_2C_6H_4$, **e**: Ar = 3-BrC_6H_4, **f**: Ar = 4-MeC_6H_4

Scheme-I: Preparation of compounds (**3a-f**)

General procedure for the preparation of 2-arylpyrimido[4',5':4,5]thiazolo [3,2-a]benzimidazol-4(3*H*)-ones (3a-f): To a solution of 3-aminothiazolo[3,2-a]benzimidazol-2-carboxamide (**1**)[4] (3 mmol) in boiling glacial acetic acid (30 mL), the appropriate aromatic aldehyde (4 mmol) was added. The reaction mixture was heated under reflux for 4-5 h. After the completion of the reaction (monitored by TLC, *n*-hexane:ethyl acetate, 70:30), the mixture was cooled to room temperature and subsequently neutralized by 10 % NaOH solution. The crude product was collected and recrystallized from ethanol to give compounds (**3a-f**) in high yields.

2-Phenylpyrimido[4',5':4,5]thiazolo[3,2-a]benzimidazol-4(3*H*)-one (3a): Yield 75 %, m.p. > 400 ºC (Lit[3]. > 400 ºC).

2-(3-Chlorophenyl)pyrimido[4',5':4,5]thiazolo[3,2-a]benzimidazol-4(3*H*)-one (3b): Yield 79 %, m.p. 387-389 ºC (Lit[3]. 391-394 ºC).

2-(4-Chlorophenyl)pyrimido[4',5':4,5]thiazolo[3,2-a]benzimidazol-4(3*H*)-one (3c): Yield 80 %, m.p. 378-381 ºC (Lit[3]. 383-385 ºC).

2-(3-Nitrophenyl)pyrimido[4',5':4,5]thiazolo[3,2-a]benzimidazol-4(3*H*)-one (3d): Yield 82 %, m.p. > 400 ºC (Lit[3]. > 400 ºC).

2-(3-Bromophenyl)pyrimido[4',5':4,5]thiazolo[3,2-a]benzimidazol-4(3*H*)-one (3e): Yield 81 %, m.p. 389-391 ºC; FT IR (KBr, ν_{max}, cm^{-1}): 3231 (NH), 1662 (C=O). ^{1}H NMR (DMSO-d_6): δ 7.4-8.2 (m, 8H, aromatic ring H), 13.12 (br, 1H, NH). MS: m/z 398 (M^+ + 2), 396 (M^+).

2-(4-Methylphenyl)pyrimido[4',5':4,5]thiazolo[3,2-a]benzimidazol-4(3*H*)-one (3f): Yield 78 %, m.p. 377-379 ºC; FT IR (KBr, ν_{max}, cm^{-1}): 3208 (NH), 1666 (C=O). ^{1}H NMR (DMSO-d_6): δ 2.4 (s, 3H, Me), 7.2-8.4 (m, 8H, aromatic ring H), 13.2 (br, 1H, NH). MS: m/z 332 (M^+).

Treatment of 3-aminothiazolo[3,2-a]benzimidazol-2-carboxamide (**1**) with aromatic aldehydes in refluxing glacial acetic acid gave products identified as 2-arylpyrimido-[4',5':4,5]thiazolo[3,2-a]benzimidazol-4(3*H*)-ones (**3a-f**). Under these conditions, attempts to isolate the intermediates 2-aryl-2,3-dihydropyrimido[4',5':4,5]thiazolo-[3,2-a]benzimidazol-4(1*H*)-ones (**2a-f**) failed when we carefully monitored the reactions. The formation of the products (**3a-f**) was assumed to proceed *via* a cyclocondensation reaction followed by air oxidation of the intermediates (**2a-f**) (**Scheme-I**).

The structure of new products (**3e** and **3f**) were established from their spectral data and for known compounds (**3a-d**) by comparison with authentic samples. For example, the IR spectrum of (**3f**) did not exhibit the stretching vibration bands at

3448, 3363 and 3196 cm^{-1} due to precursor but showed a sharp band at 3208 cm^{-1} for NH vibration. The ^1H NMR spectrum in DMSO-d_6 showed the disappearance of two broad 2H signals belonging to NH_2 moieties of compound (**1**) and the appearance of a broad 1H (NH) signal at δ 13.2 ppm which was removed on deuteration along with a multiplet at δ 7.2-8.4 ppm due to 8 aromatic protons as well as a singlet at 2.4 ppm for methyl group. Also, the molecular ion of compound (**3f**) was observed at m/z 332 (M^+), corresponding to the m.f. $C_{18}H_{12}N_4OS$.

In conclusion, we have described a new route to the synthesis of 2-arylpyrimido-[4',5':4,5]thiazolo[3,2-a]benzimidazol-4(3*H*)-ones (**3a-f**) through heterocyclization of 3-aminothiazolo[3,2-a]benzimidazol-2-carboxamide (**1**) with aromatic aldehydes in boiling glacial acetic acid followed by air oxidation.

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