Reaction of 2-amino-4-aryl-3,4-dihydro[1,3,5]triazino[1,2-a]-benzimidazoles with diethyl ethoxymethylenemalonate

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Abstract
The reaction of 2-amino-4-aryl-3,4-dihydro[1,3,5]triazino[1,2-a]-benzimidazoles with diethyl ethoxymethylenemalonate was found to afford 6-aryl-3-carbethoxy-4-oxo-4,6-dihydro-1(12)(13)H-pyrimido[2',1':4,5][1,3,5]triazino[1,2-a]benzimidazoles. The structure of the compounds obtained was established using NMR spectroscopy, including 2D NOESY experiments.

Key words: triazines, benzimidazoles, pyrimidines, cyclization.

Introduction
Diethyl ethoxymethylenemalonate (DEEM) is well known as a valuable synthone for the preparation of heterocyclic compounds [1]. The synthesis of 2-amino-3,4-dihydro[1,3,5]triazino[1,2-a]-benzimidazoles was first reported in 1970 [2]. However, only a limited number of works [3] has reported the use of these compounds as building blocks. In this communication we report the synthesis of 2-amino-4-phenyl-3,4-dihydro[1,3,5]triazino[1,2-a]-benzimidazoles and their reaction with DEEM.

Results and Discussion
The 2-amino-4-aryl-3,4-dihydro[1,3,5]triazino[1,2-a]-benzimidazoles (2) were synthesized from 2-benzimidazolylguanidine (1) and arylaldehydes according to the previously reported general method [4-6] (Scheme 1). The structure of the compounds obtained was confirmed by NMR spectroscopic studies. The preparation of 2-amino-4-phenyl-3,4-dihydro[1,3,5]triazino[1,2-a]-benzimidazole (2a) and fluorinated derivatives 2d and 2g was described in our earlier works [4,5] and [6], respectively.
Theoretically, the cyclization reaction of 2-amino-4-aryl-3,4-dihydro[1,3,5]triazino[1,2-a]-benzimidazoles (2) with DEEM may proceed in several ways (Scheme 2).
Scheme 1

1 + O

2 R = H (a), Me (b), OMe (c), F (d), Cl (e), Br (f), CF3 (g)

Scheme 2

2 + EtOOC\text{COOEt} \rightarrow 3 \rightarrow 4

2 + EtOOC\text{COOEt} \rightarrow 5 \rightarrow 6

2 + EtOOC\text{COOEt} \rightarrow 7 \rightarrow 8

2, 9: R = H (a), Me (b), OMe (c), F (d), Cl (e), Br (f), CF3 (g)
The most probable approaches include:

1) The initial attack of endocyclic N-3 of 2-amino-4-aryl-3,4-dihydro[1,3,5]triazino[1,2-a]-benzimidazoles (2) with DEEM followed by intramolecular cyclization of the presumable intermediate 3 with formation of the heterocyclic system 4.

2) The initial attack of endocyclic N-1 of 2-amino-4-aryl-3,4-dihydro[1,3,5]triazino[1,2-a]-benzimidazoles (2) with DEEM followed by intramolecular cyclization of the presumable intermediate 5 with formation of the heterocyclic system 6.

3) The initial attack of exocyclic amino group nitrogen of 2-amino-4-aryl-3,4-dihydro[1,3,5]triazino[1,2-a]-benzimidazoles (2) with DEEM followed by ring closure of the presumable intermediate 7 to N-3 or N-1 with formation of the heterocyclic system 8 or 9, respectively.

The structure 4 was ruled out based on 2D NOESY spectral data: no cross-peak was found for singlets of the sterically close protons of the triazine and pyrimidine ring.

Two pairs of annular tautomeric forms with N-H proton located at pyrimidine or triazine ring were deemed possible for structures 6 and 8 and three forms for system 9. The broadening of some signals in $^{13}$C NMR spectra of the compounds obtained was observed. The broad signals correspond to the carbon atoms located in close proximity with the nitrogen atoms involved in the tautomerism. The broad signals that was found for some atom of benzimidazole nucleus made it possible to exclude the formation of structures 6 and 8. The prototropic interconversion between three tautomeric forms of 4,6-dihydro-1(12)(13)$^H$-pyrimido[2',1':4,5][1,3,5]triazino[1,2-a]benzimidazole heterocyclic system (Scheme 3) led to the broadening of the signals of C-2, C-11, C-12a, 13a and especially C-11a in the $^{13}$C NMR spectra of 9. An additional evidence proving the assignment of structure 9 was a significant (~1 ppm) downfield shift of the signal of triazine C-H proton in the $^1$H NMR spectra of compounds 9 that was attributed to the anisotropic effect of the spatially close carbonyl group oxygen.

Scheme 3
In conclusion, a new cyclization of 2-amino-4-aryl-3,4-dihydro[1,3,5]triazino[1,2-a]-benzimidazoles and DEEM as well as detail structural analyses of the compounds obtained were reported.

**Experimental procedures**

Melting points (uncorrected) were determined on a Gallenkamp melting point apparatus. NMR spectra were recorded on a Bruker DPX-300 spectrometer, using DMSO-$d_6$ as a solvent and TMS as an internal reference.

**Synthesis of 2-amino-4-aryl-3,4-dihydro[1,3,5]triazino[1,2-a]-benzimidazoles (2).**

A solution of 2-benzimidazolylguanidine (1) (1.75 g, 10.0 mmol), appropriate substituted benzaldehyde (10.0 mmol) and 0.5 ml piperidine in ethanol (30-50 mL) was heated under reflux for 1-4 h. After cooling, the product was filtered, washed with ethanol, dried and recrystallized from DMF/ethanol.

**2-Amino-4-(4-methylphenyl)-3,4-dihydro[1,3,5]triazino[1,2-a]-benzimidazoles (2b).**

Yield 84%, mp 278-279ºC.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ 2.27 (3H, s, Me), 6.41 (2H, s, NH$_2$), 6.70 (1H, s, H-4), 6.71 (1H, d, J = 7.9 Hz, H-9), 6.78 (1H, td, J = 7.5, 1.1 Hz, H-8), 6.92 (1H, td, J = 7.5, 1.1 Hz, H-7), 7.19 (2H, d, J = 8.2 Hz, H-3’ and H-5’), 7.22 (1H, d, J = 7.9 Hz, H-6), 7.25 (2H, d, J = 8.2 Hz, H-2’ and H-6’), 8.00 (1H, s, NH).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 20.6 (Me), 65.7 (C-4), 108.2 (C-6), 115.8 (C-9), 118.9 (C-8), 120.7 (C-7), 126.1 (C-2’ and C-6’), 129.3 (C-3’ and C-5’), 131.1 (C-5a), 137.5* (C-1’), 138.6* (C-4’), 143.1 (C-9a), 153.5 (C-10a), 155.4 (C-2); *- assignments may be reversed.

**2-Amino-4-(4-methoxylphenyl)-3,4-dihydro[1,3,5]triazino[1,2-a]-benzimidazoles (2c).**

Yield 70%, mp 247-248ºC.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ 3.72 (3H, s, OMe), 6.72 (1H, d, J = 7.5 Hz, H-9), 6.76 (1H, s, H-4), 6.79 (1H, t, J = 7.5 Hz, H-8), 6.93 (1H, td, J = 7.7 Hz, H-7), 6.93 (2H, s, NH$_2$), 6.94 (2H, d, J = 8.7 Hz, H-3’ and H-5’), 7.18 (1H, d, J = 7.9 Hz, H-6), 7.34 (2H, d, J = 8.7 Hz, H-2’ and H-6’), 8.42 (1H, s, NH).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 55.1 (OMe), 65.5 (C-4), 108.3 (C-6), 114.1 (C-3’ and C-5’), 115.7 (C-9), 118.8 (C-8), 120.7 (C-7), 127.7 (C-2’ and C-6’), 131.2 (C-5a), 132.4 (C-1’), 143.1 (C-9a), 153.5 (C-10a), 155.5 (C-2), 159.7 (C-4’).

**2-Amino-4-(4-chlorophenyl)-3,4-dihydro[1,3,5]triazino[1,2-a]-benzimidazoles (2e).**

Yield 68%, mp 247-248ºC.
\textbf{1H NMR (300 MHz, DMSO-\textit{d}_6):} \delta 6.62 (2H, s, NH$_2$), 6.79 (1H, d, \(J = 7.0\) Hz, H-9), 6.82 (1H, t, \(J = 7.5\) Hz, H-8), 6.82 (1H, s, H-4), 6.94 (1H, td, \(J = 7.2, 2.3\) Hz, H-7), 7.23 (1H, d, \(J = 7.9\) Hz, H-6), 7.38 (2H, d, \(J = 8.5\) Hz, H-2' and H-6'), 7.47 (2H, d, \(J = 8.5\) Hz, H-3' and H-5'), 8.22 (1H, s, NH).

\textbf{13C NMR (75 MHz, DMSO-\textit{d}_6):} \delta 65.0 (C-4), 108.0 (C-6), 116.0 (C-9), 118.9 (C-8), 120.8 (C-7), 128.0 (C-2' and C-6'), 128.9 (C-3' and C-5'), 131.0 (C-5a), 133.6 (C-4'), 139.4 (C-1'), 143.3 (C-9a), 153.3 (C-10a), 155.2 (C-2); * - assignments may be reversed.

\textbf{2-Amino-4-(4-bromophenyl)-3,4-dihydro[1,3,5]triazino[1,2-a]-benzimidazoles (2f).}
Yield 74%, mp 254-255°C.

\textbf{1H NMR (300 MHz, DMSO-\textit{d}_6):} \delta 6.70 (2H, s, NH$_2$), 6.79 (1H, d, \(J = 7.5\) Hz, H-9), 6.82 (1H, s, H-4), 6.82 (1H, t, \(J = 7.0\) Hz, H-8), 6.95 (1H, td, \(J = 7.0, 2.3\) Hz, H-7), 7.23 (1H, d, \(J = 7.9\) Hz, H-6), 7.31 (2H, d, \(J = 8.3\) Hz, H-2' and H-6'), 7.60 (2H, d, \(J = 8.3\) Hz, H-3' and H-5'), 8.31 (1H, s, NH).

\textbf{13C NMR (75 MHz, DMSO-\textit{d}_6):} \delta 65.0 (C-4), 108.1 (C-6), 115.9 (C-9), 119.0 (C-8), 120.8 (C-7), 122.2 (C-4'), 128.3 (C-2' and C-6'), 131.0 (C-5a), 131.8 (C-3' and C-5'), 139.8 (C-1'), 143.2 (C-9a), 153.3 (C-10a), 155.2 (C-2).

\textbf{Reaction of 2-amino-4-aryl-3,4-dihydro[1,3,5]triazino[1,2-a]benzimidazoles (2) with DEEM.}
A solution of appropriate 2-amino-4-aryl-3,4-dihydro[1,3,5]triazino[1,2-a]benzimidazoles (2) (2.5 mmol) and DEEM (0.5 mL, 2.5 mmol) in DMF (15 mL) was heated under reflux for 3-5 h. After cooling, the product was filtered, washed with ethanol, dried and recrystallized from DMF.

\textbf{3-Carbethoxy-4-oxo-6-phenyl-4,6-dihydro-1(12)(13)H-pyrimido[2',1':4,5][1,3,5]triazino[1,2-a]benzimidazole (9a).}
Yield 68%, mp 319-320°C.

\textbf{1H NMR (300 MHz, DMSO-\textit{d}_6):} \delta 1.22 (3H, dd, \(J = 7.1, 7.1\) Hz, CH$_2$CH$_3$), 4.12 (1H, dq, \(J = 13.9, 7.1\) Hz, CH$_2$CH$_3$), 4.16 (1H, dq, \(J = 13.9, 7.1\) Hz, CH$_2$CH$_3$), 7.17 (1H, td, \(J = 7.2, 1.1\) Hz, H-9), 7.22 (1H, td, \(J = 7.2, 1.1\) Hz, H-10), 7.32-7.41 (4H, m, H-11, H-3', H-4' and H-5'), 7.54 (2H, dd, \(J = 7.9, 1.9\) Hz, H-2' and H-6'), 7.60 (1H, dd, \(J = 7.2, 1.1\) Hz, H-8), 8.05 (1H, s, H-6), 8.47 (1H, s, H-2), 13.12 (1H, br s, NH).

\textbf{13C NMR (75 MHz, DMSO-\textit{d}_6):} \delta 14.1 (Me), 59.5 (CH$_2$), 65.1 (C-6), 105.4 (C-3), 110.5 (C-8), 112.8 (C-11), 122.8 (C-10), 123.8 (C-9), 126.6 (C-2' and C-6'), 128.2 (C-7a), 129.0 (C-3' and C-5'), 129.7 (C-4'), 132.3 (C-11a), 137.3 (C-1'), 149.2 (C-13a), 154.9 (C-12a), 156.8 (C-4), 160.3 (C-2), 163.3 (COOEt).

\textbf{3-Carbethoxy-6-(4-methylphenyl)-4-oxo-4,6-dihydro-1(12)(13)H-pyrimido[2',1':4,5][1,3,5]triazino[1,2-a]benzimidazole (9b).}
Yield 72%, mp 322-323°C.
$^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 1.22 (3H, dd, $J = 7.2, 7.2$ Hz, $CH_2CH_3$), 2.21 (3H, s, ArMe), 4.12 (1H, dq, $J = 10.9, 7.2$ Hz, $CH_2CH_3$), 4.16 (1H, dq, $J = 10.9, 7.2$ Hz, $CH_2CH_3$), 7.16 (2H, d, $J = 8.1$ Hz, H-3' and H-5'), 7.17 (1H, td, $J = 7.5, 1.1$ Hz, H-9), 7.22 (1H, td, $J = 7.5, 1.1$ Hz, H-10), 7.37 (1H, d, $J = 7.9$ Hz, H-11), 7.40 (2H, d, $J = 8.1$ Hz, H-2' and H-6'), 7.57 (1H, dd, $J = 7.5, 1.1$ Hz, H-8), 7.99 (1H, s, H-6), 8.45 (1H, s, H-2), 13.07 (1H, br s, NH).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 14.1 (Me), 20.6 (ArMe), 59.5 (CH$_2$), 64.9 (C-6), 105.5 (C-3), 110.5 (C-8), 112.7 (C-11), 122.7 (C-10), 123.7 (C-9), 126.5 (C-2' and C-6'), 128.2 (C-7a), 128.4 (C-11a), 134.4 (C-1'), 139.4 (C-4'), 149.2 (C-13a), 154.8 (C-12a), 156.7 (C-4), 160.1 (C-2), 163.4 (COOEt).

Yield 51%, mp 305-306ºC.

$^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 1.23 (3H, dd, $J = 7.2, 7.2$ Hz, $CH_2CH_3$), 3.69 (3H, s, OMe), 4.13 (1H, dq, $J = 10.9, 7.2$ Hz, $CH_2CH_3$), 4.18 (1H, dq, $J = 10.9, 7.2$ Hz, $CH_2CH_3$), 6.90 (2H, d, $J = 8.6$ Hz, H-3' and H-5'), 7.18 (1H, t, $J = 7.5$ Hz, H-9), 7.23 (1H, t, $J = 7.2$ Hz, H-10), 7.39 (1H, d, $J = 7.5$ Hz, H-11), 7.47 (2H, d, $J = 8.6$ Hz, H-2' and H-6'), 7.58 (1H, d, $J = 7.5$ Hz, H-8), 8.00 (1H, s, H-6), 8.47 (1H, s, H-2), 12.84 (1H, br s, NH).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 14.1 (Me), 55.1 (OMe), 59.5 (CH$_2$), 64.7 (C-6), 105.4 (C-3), 110.5 (C-8), 112.7 (C-11), 122.7 (C-10), 123.7 (C-9), 126.5 (C-2' and C-6'), 128.2 (C-7a), 129.4 (C-11a), 149.2 (C-13a), 154.8 (C-12a), 156.7 (C-4'), 160.1 (C-2), 163.4 (COOEt).

3-Carbethoxy-6-(4-fluorophenyl)-4-oxo-4,6-dihydro-1(12)(13)H-pyrimido[2',1':4,5]-[1,3,5]triazino[1,2-a]benzimidazole (9d).
Yield 65%, mp 309-310ºC.

$^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 1.22 (3H, dd, $J = 7.2, 7.2$ Hz, $CH_2CH_3$), 4.13 (1H, dq, $J = 10.9, 7.2$ Hz, $CH_2CH_3$), 4.16 (1H, dq, $J = 10.9, 7.2$ Hz, $CH_2CH_3$), 7.15-7.26 (4H, m, H-9, H-10, H-3' and H-5'), 7.39 (1H, d, $J = 7.2$ Hz, H-11), 7.47 (2H, d, $J = 8.6$ Hz, H-2' and H-6'), 7.58 (1H, d, $J = 7.5$ Hz, H-8), 8.00 (1H, s, H-6), 8.47 (1H, s, H-2), 12.84 (1H, br s, NH).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 14.1 (Me), 59.5 (CH$_2$), 64.7 (C-6), 105.4 (C-3), 110.5 (C-8), 112.7 (C-11), 114.2 (C-3' and C-5'), 122.7 (C-10), 123.7 (C-9), 126.5 (C-2' and C-6'), 128.2 (C-7a), 129.4 (C-11a), 149.2 (C-13a), 154.8 (C-12a), 156.7 (C-4'), 160.2 (C-2), 163.4 (COOEt).

3-Carbethoxy-6-(4-chlorophenyl)-4-oxo-4,6-dihydro-1(12)(13)H-pyrimido[2',1':4,5]-[1,3,5]triazino[1,2-a]benzimidazole (9e).
Yield 70%, mp 318-319ºC.
$^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 1.23 (3H, dd, $J = 7.0, 7.0$ Hz, CH$_2$CH$_3$), 4.13 (1H, dq, $J = 14.2, 7.0$ Hz, CH$_2$CH$_3$), 4.17 (1H, dq, $J = 14.2, 7.0$ Hz, CH$_2$CH$_3$), 7.19 (1H, td, $J = 7.5, 1.1$ Hz, H-9), 7.24 (1H, td, $J = 7.5, 1.1$ Hz, H-10), 7.40 (1H, dd, $J = 7.2, 1.1$ Hz, H-11), 7.45 (2H, d, $J = 8.3$ Hz, H-3' and H-5'), 7.60 (2H, d, $J = 8.7$ Hz, H-2' and H-6'), 7.60 (1H, d, $J = 7.2$ Hz, H-8), 8.07 (1H, s, H-6), 8.49 (1H, s, H-2), 13.22 (1H, br s, NH).

$^{13}$C NMR (75 MHz, DMSO-d$_6$): $\delta$ 14.2 (Me), 59.5 (CH$_2$), 64.6 (C-6), 105.5 (C-3), 110.5 (C-8), 112.9 (C-11), 122.8 (C-10), 123.9 (C-9), 128.1 (C-7a), 128.7 (C-2' and C-6'), 129.0 (C-3' and C-5'), 132.4 (C-11a), 134.4 (C-1'), 136.2 (C-4'), 149.1 (C-13a), 154.6 (C-12a), 156.8 (C-4), 160.2 (C-2), 163.3 (COOEt).

6-(4-Bromophenyl)-3-carbethoxy-4-oxo-4,6-dihydro-1(12)(13)H-pyrimido[2',1':4,5]-[1,3,5]triazino[1,2-a]benzimidazole (9f).

Yield 68%, mp 320-321ºC.

$^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 1.22 (3H, dd, $J = 7.0, 7.2$ Hz, CH$_2$CH$_3$), 4.12 (1H, dq, $J = 14.5, 7.2$ Hz, CH$_2$CH$_3$), 4.17 (1H, dq, $J = 14.5, 7.2$ Hz, CH$_2$CH$_3$), 7.19 (1H, td, $J = 7.5, 1.1$ Hz, H-9), 7.24 (1H, td, $J = 7.5, 1.1$ Hz, H-10), 7.40 (1H, d, $J = 7.2$ Hz, H-11), 7.52 (2H, d, $J = 8.7$ Hz, H-3' and H-5'), 7.59 (2H, d, $J = 8.7$ Hz, H-2' and H-6'), 7.60 (1H, d, $J = 7.2$ Hz, H-8), 8.05 (1H, s, H-6), 8.48 (1H, s, H-2), 13.21 (1H, br s, NH).

$^{13}$C NMR (75 MHz, DMSO-d$_6$): $\delta$ 14.1 (Me), 59.5 (CH$_2$), 64.7 (C-6), 105.4 (C-3), 110.5 (C-8), 112.9 (C-11), 122.8 (C-10), 123.1 (C-4'), 123.9 (C-9), 128.1 (C-7a), 128.9 (C-2' and C-6'), 132.0 (C-3' and C-5'), 132.4 (C-11a), 136.6 (C-1'), 149.1 (C-13a), 154.6 (C-12a), 156.8 (C-4), 160.2 (C-2), 163.3 (COOEt).

3-Carbethoxy-4-oxo-6-(4-trifluoromethylphenyl)-4,6-dihydro-1(12)(13)H-pyrimido[2',1':4,5]-[1,3,5]triazino[1,2-a]benzimidazole (9g).

Yield 72%, mp 311-312ºC.

$^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 1.22 (3H, dd, $J = 7.0, 7.2$ Hz, CH$_2$CH$_3$), 4.12 (1H, dq, $J = 10.6, 7.2$ Hz, CH$_2$CH$_3$), 4.17 (1H, dq, $J = 10.6, 7.2$ Hz, CH$_2$CH$_3$), 7.19 (1H, t, $J = 7.5$ Hz, H-9), 7.24 (1H, t, $J = 7.5$ Hz, H-10), 7.40 (1H, d, $J = 7.2$ Hz, H-11), 7.62 (1H, d, $J = 7.2$ Hz, H-8), 7.77 (2H, d, $J = 8.7$ Hz, H-3' and H-5'), 7.82 (2H, d, $J = 8.7$ Hz, H-2' and H-6'), 8.15 (1H, s, H-6), 8.48 (1H, s, H-2), 13.27 (1H, br s, NH).

$^{13}$C NMR (75 MHz, DMSO-d$_6$): $\delta$ 14.1 (Me), 59.6 (CH$_2$), 64.7 (C-6), 105.4 (C-3), 110.4 (C-8), 113.0 (C-11), 122.9 (C-10), 123.6 (q, $J = 272.6$ Hz, CF$_3$), 123.9 (C-9), 126.0 (q, $J = 3.8$ Hz, C-3' and C-5'), 127.8 (C-2' and C-6'), 128.1 (C-7a), 130.0 (q, $J = 31.8$ Hz, C-4'), 132.4 (C-11a), 141.4 (C-1'), 149.1 (C-13a), 154.6 (C-12a), 156.8 (C-4), 160.1 (C-2), 163.2 (COOEt).

References


