



Reactivity of asymmetric benzo-condensed diazines with nitrilimine dipoles in the 1,3-dipolar cycloaddition reactions

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ABSTRACT

The reactivity of asymmetric benzo-condensed diazines in the 1,3-dipolar cycloaddition reactions with nitrilimines was investigated. The results demonstrated that, at variance with the symmetric quinoxaline, a certain grade of diastereoselectivity emerged. Moreover in the case of the 5-methylquinoxaline and quinoxaline a mono-cycloadduct was obtained.

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The 1,3-dipolar cycloaddition reactions (1,3-DCRs), involving heterocyclic rings as 2π components, have been largely studied as useful synthetic strategy to obtain various heterocyclic systems. In particular azine or diazine systems (pyridine, quinoline, isoquinoline, pyrazine, benzodiazepine) have shown to undergo 1,3-DCRs highly site- and regio-selective with different 1,3-dipoles (nitrilimines, nitriloxides, nitrilylides).^{1–3} All the examples of 1,3-DCRs to quinoxaline ring reported in the literature have demonstrated that the dipoles react exclusively at C=N bonds (site-selectivity) leaving the C=C bonds intact and always by keeping the same orientation (regio-selectivity).^{4,5}

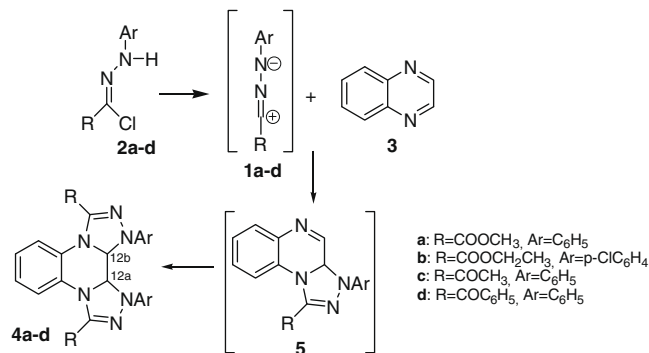
Recently a study on quinoxaline behaviour in the 1,3-DCRs with nitrilimines was reported.⁶ The 1,3-DCRs of nitrilimines **1**, generated in situ from chloroarylhydrazones **2**, to quinoxaline (**3**) are highly site- and regio-selective but not diastereoselective (Scheme 1).

In fact, experimental results demonstrated that, in each case, all possible diastereoisomeric bis-cycloadducts **4** (RR, SS, and meso form RS) were obtained. Specific studies to establish their exact stereochemical configuration were carried out, by using CLSRs (Chiral Lanthanide Shift Reagent) in NMR analysis.⁶ These findings furthermore confirmed the lack of diastereoselectivity contrary to the literature reports for other symmetrical diazine rings.^{2,7} Further, in contrast with the data reported by Dalla Croce,⁵ the formation of the corresponding monoadduct **5** has been never observed. An explanation for this behavior could be the higher reactivity of

the mono-cycloadduct formed in the first step or the synchronous formation of the two triazole rings.⁴

With the aim of investigating the reactivity of asymmetric benzodiazines in 1,3-DCRs with nitrilimines, our studies were extended to the 2-methylquinoxaline, 5-methylquinoxaline, and quinoxaline systems. The reactions of chloroarylhydrazones **2a–d** with 2-methylquinoxaline (**6**), under analogous experimental conditions used in the reaction involving quinoxaline (**3**), yielded only the racemic mixture (RR, SS) **7a–d** in low yield (Scheme 2).⁸

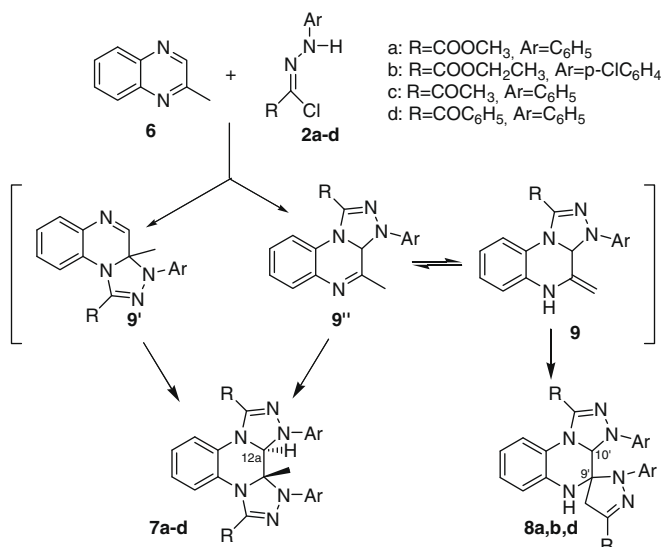
For these derivatives, in the ¹H NMR spectrum, the chemical shifts, for the 12a position atoms, were found in the range 5.54–5.90 ppm. These values are in agreement with the signals of the corresponding position in the symmetric anti diastereoisomers



Scheme 1. Reactivity of quinoxaline in the 1,3-DCRs with nitrilimine dipoles.

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Scheme 2. Reactivity of 2-methylquinoxaline in the 1,3-DCRs with nitrilimine dipoles.

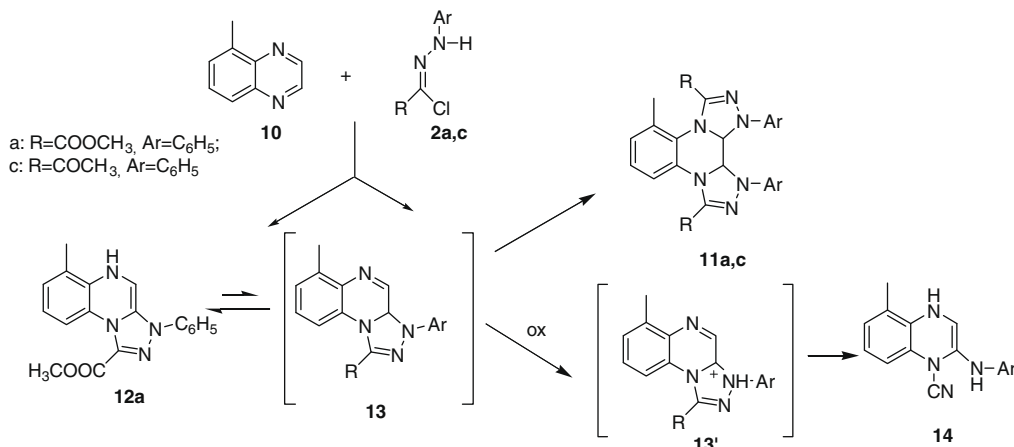
4.⁶ The experimental results evidence that the presence of the methyl group, on the reaction site, decreases the quinoxaline ring reactivity as dipolarophile but leads to a certain grade of diastereoselectivity in the reaction. Moreover from the reaction mixture (Scheme 2) 2,1'-diaryl-2,4,1',10'a-tetrahydro-9*H*-spiro{pyrazolo-3,10'-[1,2,4]triazolo[4,3-*a*]quinoxaline} spiro-cycloadduct of type **8** was isolated. Its formation could be explained with the cycloaddition of the 1,3-dipoles to the exocyclic enaminic C=C bond of the mono-cycloadduct in the tautomeric form **9**. This tautomer is originated from mono-cycloadduct **9'** formed upon addition of nitrilimine dipoles on the unsubstituted C=N bond. Since the spiro compound formation competes against the second cycloaddition reaction and for this reason the yields decrease. This represents the first example of spiro substituted triazoloquinoxaline derivative reported.

From these results one point clearly emerged: in spite of the presence of the methyl group in the reaction site, the mono-cycloadduct was not isolated. Only a different diastereoselectivity of the reaction was observed. On the contrary, in the case of the 5-methylquinoxaline, its asymmetry can be considered different. In fact the influence of the methyl group, in this case, has to be

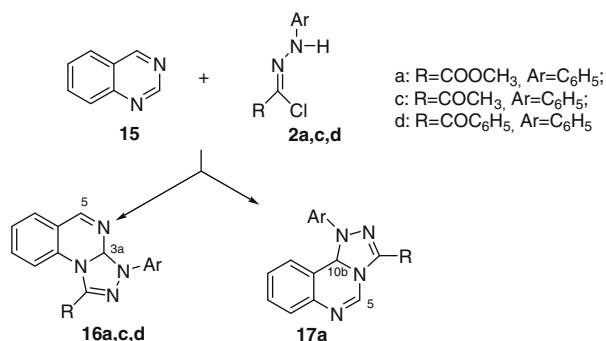
considered 'long range' because it does not influence directly the atoms implicated in the cycloaddition. Thus, from the reaction of 5-methylquinoxaline (**10**) and chloroarylhydrazones **2a,c**, under the usual experimental conditions, 1,12-diphenyl-5-methyl-1,12,12a,12b-tetrahydrobis[1,2,4]triazolo[4,3-*a*:3',4'-*c*]quinoxaline bis-cycloadducts of type **11**, were isolated in low yields.⁸ In this case, due to the presence of the methyl group in position 5, it was possible to measure the coupling constant between H-12a and H-12b ($J = 7.4\text{--}7.6\text{ Hz}$). This value, according to Karplus rule, is in agreement with a dihedral angle typical of an anti configuration. Furthermore, in this case as well, the chemical shifts observed for the position 12, in the ¹H NMR spectrum, are comparable with the corresponding signals for the symmetric tetrahydrobis-triazoloquinoxaline derivatives in the *anti* configuration.⁴ Moreover from the reaction mixture it was possible to isolate methyl 6-methyl-3-phenyl-3,5-dihydro[1,2,4]triazolo[4,3-*a*]quinoxaline-1-carboxylate mono-cycloadduct (**12a**) (Scheme 3).

In this case, because of the tautomeric equilibrium involving the mono-cycloadduct **13**, the formation of the bis-cycloadduct **11** competes with the 3,5-dihydro form **12a**. In fact the electron-donating feature of the methyl moiety favors the enaminic form **12a** compared to the iminic form **13**, forbidding the second cycloaddition. Moreover it was possible to isolate the 1-carbonitrile-5-methyl-2-phenylimino-2*H*-quinoxaline (**14**). The formation of this compound could be rationalized on the basis of the literature data concerning the action of nucleophiles on the oxidized quinoline cycloadduct **13'**.⁹ On the basis of these experimental evidences, regarding the 1,3-DCRs of the 5-methyl-quinoxaline with the nitrilimine dipoles, it is possible to conclude that the presence of the methyl group is determinant for the partial change of the reaction pathway. In fact, the structural asymmetry allowed to obtain mono-cycloadducts **12a**, not isolated before. The second cycloaddition reaction is partially forbidden because of the tautomeric equilibrium leading to the 3,5-dihydro tautomer of type **12**. Therefore it was evidenced that the introduction of the asymmetry changes the reaction pathway. The next step was to introduce the asymmetry element directly in the core of the benzodiazine. Thus to extend the study on the reactivity of the asymmetric benzo-condensed diazine, we realized analogous 1,3-DCRs on the quinazoline (**15**) as dipolarophile (Scheme 4).⁸

In all the reactions, the formation of phenyl-1,10b-dihydro-[1,2,4]triazolo[4,3-*c*]quinazoline mono-cycloadducts of type **16** was evidenced. Only in the reaction with **2a** the reaction was not site-selective and the isomer derived from cycloaddition on 3–4 bond, 1-carbomethoxy-3-phenyl-3,3a-dihydro-[1,2,4]triazolo[4,3-



Scheme 3. Reactivity of 5-methylquinoxaline in the 1,3-DCRs with nitrilimine dipoles.



Scheme 4. Reactivity of quinoxaline in the 1,3-DCRs with nitrilimine dipoles.

c]quinoxaline (**17a**), was also isolated. It revealed the same site-selectivity observed with the more nucleophile dipoles in pyrimidine series (preferential cycloaddition on 1–2 position).¹⁰

The analysis of the experimental data showed that the cycloaddition reactions, involving the dipole nitrilimines as dipoles and the asymmetric benzodiazines as dipolarophiles, lead to a reaction route different from that observed in the case of symmetric benzodiazines. First the reactivity lowers and also a certain grade of diastereoselectivity emerged. In other words the asymmetric feature 'generates' a diastereoisomer simplification because the *syn* configuration partially is forbidden. In fact, only in the case of the dipole higher reactive, the *syn* diastereoisomer was isolated.

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- Experimental data:** All melting points were taken on a Buchi-Tottoli capillary apparatus and are uncorrected; IR spectra were determined in bromoform with a Jasco FT/IR 5300 spectrophotometer; ¹H and ¹³C NMR spectra were measured in CDCl₃ solution (TMS as internal reference) at 200 and 50.3 MHz, respectively, using a Bruker AC-E series 200 MHz spectrometer. ¹³C NMR spectra are reported, indicating the multiplicity, (s, singlet; d, doublet; t, triplet; q, quartet) assigned by DEPT135 experiments. Column chromatography was performed with Merck silica gel 230–400 mesh ASTM or with a Biotage FLASH40i chromatography module (prepacked cartridge system). General procedure for the 1,3-dipolar cycloaddition of 2-methylquinoxaline (**6**) and chlorophenylhydrazones **2a–d**. Triethylamine 1.15 mL (8.3 mmol) was added to a solution of 2-methylquinoxaline (3.47 mmol) and chlorophenylhydrazones (6.93 mmol) in anhydrous tetrahydrofuran (20 mL). The mixture was stirred at room temperature for appropriate time (**2a,b**, 60 h; **2c,d**, 72 h). The chlorhydrate of triethylamine was removed by filtration and the solution was evaporated under reduced pressure. The residue was washed with ethanol (5 mL) and chromatographed on a silica gel column using dichloromethane as the eluent. In the reaction with **2a**, the first fraction eluted gave 3,10-dimethoxycarbonyl-1,12-diphenyl-12a-methyl-1,12,12a,12b-tetrahydrobis[1,2,4]triazolo[4,3-*a'*:3',4'-c]quinoxaline (**7a**): yield 30%; mp 187–188 °C; IR cm⁻¹ 1735 (C=O); ¹H NMR: δ 1.32 (s, 3H, CH₃), 3.88 (s, 3H, CH₃), 3.95 (s, 3H, CH₃), 5.85 (s, 1H, H-12b), 6.80–6.95 (m, 2H, H-5, H-8), 7.12–7.21 (m, 10H, Ar-H), 7.45–7.60 (m, 2H, H-6, H-7); ¹³C NMR: δ 14.7 (q), 52.9 (q), 53.7 (q), 75.6 (d), 78.5 (s), 114.0 (d), 118.2 (d), 119.0 (d), 121.5 (d), 122.4 (d), 122.9 (d), 123.3 (s), 123.6 (d), 123.8 (d), 124.3 (s), 128.7 (d), 129.0 (d), 141.2 (s), 141.3 (s), 141.8 (s), 145.2 (s), 158.5 (s), 158.8 (s). Anal. Calcd for C₂₇H₂₄N₆O₄: C, 65.31; H, 4.87; N, 16.93. Found: C, 65.66; H, 4.83; N, 17.00. The second fraction eluted gave dimethyl 2,1'-diphenyl-2,4,1',10a'-tetrahydro-9'H-spiro[pyrazolo-3,10'-[1,2,4]triazolo[4,3-*a'*:3',4'-c]quinoxaline]-3',5'-dicarboxylate (**8a**): yield 20%; mp 222–224 °C, from ethanol; IR cm⁻¹ 3330 (NH), 1729 and 1720 (C=O); 1594 (C=N). ¹H NMR: δ 2.27 (d, 1H, CH₂, J = 19.1 Hz), 2.98 (d, 1H, CH₂, J = 19.1 Hz), 3.73 (s, 3H, CH₃), 3.77 (s, 3H, CH₃), 5.27 (s, 1H, H-10a'), 6.67 (d, 1H, H-5', J = 8.2 Hz), 6.72 (d, 1H, p-C₆H₅), 6.95–7.02 (m, 9H, Ar-H), 7.17–7.22 (m, 2H, H-7', H-6'), 7.39 (d, 1H, H-8', J = 8.2 Hz); ¹³C NMR: δ 27.7 (t), 52.0 (q), 52.4 (q), 56.9 (d), 74.7 (s), 114.5 (d), 115.6 (d), 115.9 (d), 118.1 (s), 122.5 (d), 122.7 (d), 125.7 (d), 126.1 (d), 126.7 (d), 128.1

(d), 128.5 (d), 131.2 (s), 133.4 (s), 141.8 (s), 142.2 (s), 143.9 (s), 158.3 (s), 164.0 (s). Anal. Calcd for C₂₇H₂₄N₆O₄: C, 65.31; H, 4.87; N, 16.93. Found: C, 65.45; H, 4.82; N, 16.82. In the case of the reaction with **2b**, the first fraction eluted gave 1,12-(4-chlorophenyl)-3,10-diethoxycarbonyl-12a-methyl-1,12,12a,12b-tetrahydrobis[1,2,4]triazolo[4,3-*a'*:3',4'-c]quinoxaline (**7b**): yield 25%; mp 115–117 °C; IR cm⁻¹ 1731 (C=O); ¹H NMR: δ 1.37 (s, 3H, CH₃), 1.26–1.35 (m, 6H, 2 × CH₃), 4.30–4.77 (m, 4H, 2 × CH₂), 5.90 (s, 1H, H-12b), 7.05–7.54 (m, 12H, H-6, H-7, H-5, H-8, 2 × o-C₆H₄Cl, 2 × m-C₆H₄Cl); ¹³C NMR: δ 13.6 (q), 13.8 (q), 14.7 (q), 62.3 (t), 63.1 (t), 75.2 (d), 78.4 (s), 115.4 (d), 119.0 (d), 123.0 (d), 123.1 (s), 123.5 (d), 123.8 (2 × d), 124.1 (s), 125.2 (s), 125.9 (s), 128.6 (d), 128.8 (d), 140.1 (s), 141.2 (s), 142.3 (s), 143.7 (s), 157.8 (s), 158.8 (s). Anal. Calcd for C₂₉H₂₆Cl₂N₆O₄: C, 58.69; H, 4.42; N, 14.16. Found: C, 58.66; H, 4.48; N, 14.22. The second fraction eluted gave diethyl 2,1'-di-(4-chlorophenyl)-2,4,1',10a'-tetrahydro-9'H-spiro[pyrazolo-3,10'-[1,2,4]triazolo[4,3-*a'*:3',4'-c]quinoxaline]-3',5'-dicarboxylate (**8b**): yield 15%; mp 170–172 °C, from ethanol; IR cm⁻¹ 3322 (NH), 1731 and 1730 (C=O), 1590 (C=N); ¹H NMR: δ 1.20–1.27 (m, 6H, 2 × CH₃), 2.27 (d, 1H, CH₂, J = 19.1 Hz), 3.03 (d, 1H, CH₂, J = 19.1 Hz), 4.22–4.25 (m, 4H, 2 × CH₂), 5.25 (s, 1H, H-10a'), 6.67 (d, 2H, o-C₆H₄Cl, J = 7.4 Hz), 6.85–7.12 (m, 6H, m-C₆H₄Cl, H-5', H-6', H-7', H-8'), 7.27 (d, 2H, o-C₆H₄Cl, J = 7.8 Hz), 7.37 (d, 2H, m-C₆H₄Cl, J = 7.8 Hz); ¹³C NMR: δ 13.8 (q), 14.1 (q), 27.9 (t), 56.4 (d), 60.8 (t), 61.6 (t), 74.8 (s), 114.5 (d), 115.9 (d), 116.7 (d), 118.1 (s), 124.4 (d), 126.2 (d), 126.3 (s), 126.7 (d), 128.0 (d), 128.2 (d), 130.1 (s), 132.4 (s), 133.3 (s), 140.9 (s), 142.7 (s), 157.7 (s), 163.2 (s). Anal. Calcd for C₂₉H₂₆Cl₂N₆O₄: C, 58.69; H, 4.42; N, 14.16. Found: C, 58.66; H, 4.39; N, 14.22. In the reaction with **2c**, the residue was washed with ethanol (5 mL) and chromatographed on a silica gel column using dichloromethane as eluent. The first fraction eluted gave 3,10-diethyl-1,12-diphenyl-12a-methyl-1,12,12a,12b-tetrahydrobis[1,2,4]triazolo[4,3-*a'*:3',4'-c]quinoxaline (**7c**): yield 35%; mp 195–197 °C; IR cm⁻¹ 1685 (C=O), 1595 (C=N); ¹H NMR: δ 1.45 (s, 3H, CH₃), 2.66 (s, 3H, CH₃), 2.70 (s, 3H, CH₃), 5.54 (s, 1H, H-12b), 6.93 (t, 2H, p-C₆H₅, J = 7.0 Hz), 7.05–7.35 (m, 11H, Ar-H, H-5, H-8, H-7), 7.35 (m, 1H, H-6); ¹³C NMR: δ 15.2 (q), 28.4 (q), 28.7 (q), 77.2 (d), 80.1 (s), 114.2 (d), 118.54 (d), 120.9 (d), 122.1 (d), 122.8 (d), 123.3 (d), 122.9 (d), 124.6 (d), 124.6 (2 × s), 128.7 (d), 129.2 (d), 140.6 (s), 144.1 (s), 145.7 (s), 147.7 (s), 188.2 (s), 188.7 (s). Anal. Calcd for C₂₇H₂₄N₆O₂: C, 69.81; H, 5.21; N, 18.09. Found: C, 69.47; H, 5.15; N, 18.32. In the reaction with **2d**, the first fraction eluted gave 3,10-dibenzoyl-1,12-diphenyl-12a-methyl-1,12,12a,12b-tetrahydrobis[1,2,4]triazolo[4,3-*a'*:3',4'-c]quinoxaline (**7d**): yield 40%; mp 90–92 °C; IR cm⁻¹ 1658 (C=O), 1596 (C=N); ¹H NMR: δ 1.64 (s, 3H, CH₃), 5.67 (s, 1H, H-12b), 6.90–7.35 (m, 14H, Ar-H, H-5, H-6, H-7, H-8), 7.55–7.75 (m, 6H, m-COC₆H₅, p-COC₆H₅), 8.25 (4H, o-COC₆H₅); ¹³C NMR: δ 15.3 (q), 77.6 (d), 79.4 (s), 114.5 (d), 118.7 (d), 119.6 (d), 121.9 (d), 122.7 (d), 123.4 (d), 122.9 (d), 123.0 (d), 124.2 (2 × s), 128.6 (d), 128.7 (d), 128.6 (d), 129.2 (d), 130.4 (d), 130.6 (d), 134.1 (d), 134.8 (d), 135.5 (s), 136.3 (s), 144.7 (s), 145.2 (2 × s), 141.2 (s), 145.4 (s), 183.1 (s), 183.5 (s). Anal. Calcd for C₃₇H₂₈N₆O₂: C, 75.49; H, 4.79; N, 14.28. Found: C, 75.66; H, 4.83; N, 14.32. The second fraction eluted gave 3',5'-dibenzoyl-2,1'-diphenyl-2,4,1',10a'-tetrahydro-9'H-spiro[pyrazolo-3,10'-[1,2,4]triazolo[4,3-*a'*:3',4'-c]quinoxaline] (**8d**): yield 15%; mp 114–115 °C; IR cm⁻¹ 1644 (C=O), 1596 (C=N); ¹H NMR: δ 2.70 (d, 1H, J = 19.3 Hz, CH₂), 3.20 (d, 1H, J = 19.3 Hz, CH₂), 4.28 (s, 1H, NH), 5.32 (s, 1H, H-10'a), 6.56 (d, 1H, J = 8.2 Hz, p-C₆H₅), 6.81–7.59 (m, 19H, Ar-H), 7.80 (d, 1H, J = 8.2 Hz, H-8'), 8.17 (d, 1H, J = 8.2 Hz, H-5'); ¹³C NMR: δ 26.7 (t), 56.2 (d), 75.9 (s), 114.7 (d), 115.5 (d), 118.5 (d), 120.0 (s), 123.4 (d), 124.2 (d), 125.7 (d), 126.1 (d), 126.2 (d), 126.8 (d), 127.7 (d), 128.4 (d), 128.5 (d), 129.3 (d), 130.4 (d), 130.2 (d), 131.0 (d), 131.8 (s), 133.7 (d), 136.3 (s), 140.1 (s), 141.7 (s), 143.9 (s), 146.4 (s), 183.1 (s), 190.9 (s). Anal. Calcd for C₃₇H₂₈N₆O₂: C, 75.49; H, 4.79; N, 14.28. Found: C, 75.56; H, 4.82; N, 14.23. General procedure for the 1,3-dipolar cycloaddition of 5-methylquinoxaline (**10**) and chlorophenylhydrazones **2a,c**. Triethylamine 1.15 mL (8.3 mmol) was added to a solution of 5-methylquinoxaline (4.57 mmol, 0.66 g) and chlorophenylhydrazones (9.15 mmol) in anhydrous tetrahydrofuran (20 mL). The mixture was stirred at room temperature for 72 h (36 h in the case of the reaction with **2c**). The chlorhydrate of triethylamine was removed by filtration. The solution was evaporated under reduced pressure. The residue was washed with ethanol (5 mL) and chromatographed on a silica gel column. In the reaction with **2a**, using cyclohexane/ethyl acetate (9:1) as the eluent, the first fraction eluted gave 2-anilino-5-methylquinoxaline-1(4H)-carbonitrile (**14**): yield 22%; mp 174–175 °C; IR cm⁻¹ 2242 (CN); ¹H NMR: δ 2.54 (s, 3H, CH₃), 7.01 (m, 2H, p-C₆H₅, H-8), 7.18–7.45 (m, 6H, Ar-H), 8.12 (s, 1H, H-3). ¹³C NMR: δ 17.2 (q), 104.5 (s), 112.5 (d), 121.2 (d), 125.0 (d), 127.4 (d), 128.3 (2 × s), 129.4 (d), 131.30 (s), 131.35 (d), 139.6 (s), 141.6 (d), 145.07 (s). Anal. Calcd for C₁₆H₁₄N₄: C, 73.26; H, 5.38; N, 21.36. Found: C, 73.67; H, 5.43; N, 21.53. The second fraction eluted gave 3,10-dimethoxycarbonyl-1,12-diphenyl-5-methyl-1,12,12a,12b-tetrahydrobis[1,2,4]triazolo[4,3-*a'*:3',4'-c]quinoxaline (**11a**): yield 20%; mp 219–222 °C, from ethanol; IR cm⁻¹ 1735 (C=O), 1598 (C=N); ¹H NMR: δ 2.13 (s, 3H, CH₃), 3.82 (s, 3H, CH₃), 3.91 (s, 3H, CH₃), 5.83 (d, 1H, H-12a, J = 7.6 Hz), 5.86 (d, 1H, H-12b, J = 7.6 Hz), 6.76 (m, 2H, H-6, H-7), 7.03–7.18 (m, 11H, H-8, Ar-H); ¹³C NMR: δ 18.2 (q), 52.9 (q), 53.3 (q), 70.9 (d), 71.7 (d), 113.0 (d), 113.3 (d), 116.9 (d), 120.4 (s), 120.8 (d), 124.0 (d), 125.1 (d), 126.6 (s), 128.7 (d), 128.8 (d), 132.0 (s), 141.6 (s), 141.8 (s), 142.7 (s), 143.8 (s), 157.8 (s), 159.0 (s). Anal. Calcd for C₂₇H₂₄N₆O₄: C, 65.31; H, 4.87; N, 16.93. Found: C, 65.26; H, 4.93; N, 17.02. Further fraction eluted afforded methyl 6-methyl-3-phenyl-3,5-dihydro[1,2,4]triazolo[4,3-*a'*:3',4'-c]quinoxaline-1-carboxylate (**12a**): yield 12%; mp 202–204 °C, from ethanol; IR cm⁻¹ 3250 (N-H), 1715 (C=O), 1650 (C=N); ¹H NMR: δ 2.65 (s, 3H, CH₃), 3.86 (s, 3H, CH₃), 6.77 (d, 1H, H-9, J = 8.3 Hz), 7.05 (1H, p-C₆H₅), 7.20–7.45 (m, 6H, Ar-H), 8.18 (s, 1H, H-4), 8.39 (s, 1H, N-H). ¹³C NMR: δ 17.6 (q), 53.0 (q), 111.8 (d), 114.9 (d), 119.0 (s), 131.3 (s), 123.7 (d), 126.6 (d), 129.5 (d), 131.8 (d), 139.0 (s), 139.8 (s), 141.5 (s), 148.9 (d), 153.3 (s). Anal. Calcd for C₁₈H₁₆N₄O₂: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.54; H, 5.13; N, 17.32. In the reaction with **2c**,

the first fraction eluted, using DCM as the eluent, gave **14** (yield 20%). Further fraction afforded 3,10-diacetyl-1,12-diphenyl-5-methyl-1,12,12a,12b-tetrahydrobis[1,2,4]triazolo[4,3-*a*:3',4'-*c*]quinoxaline (**11c**): yield 25%; mp 184.7–185.3 °C, from ethanol; IR cm^{-1} 1691 (C=O), 1598 (C=N); ^1H NMR: δ 2.12 (s, 3H, CH₃), 2.64 (s, 3H, CH₃), 2.66 (s, 3H, CH₃), 5.34 (d, 1H, H-12a, $J = 7.4$ Hz), 5.58 (d, 1H, H-12b, $J = 7.4$ Hz), 6.92–7.30 (m, 13H, Ar-H; H-8, H-7, H-6); ^{13}C NMR: δ 19.0 (q), 27.2 (q), 28.7 (q), 72.9 (d), 73.8 (d), 113.6 (d), 114.0 (d), 118.6 (s), 121.4 (d), 122.0 (d), 123.7 (s), 123.9 (d), 125.3 (d), 126.7 (s), 128.9 (s), 129.1 (d), 132.2 (s), 142.3 (s), 142.7 (s), 187.7 (s), 188.6 (s). Anal. Calcd for C₂₇H₂₄N₆O₂: C, 69.81; H, 5.21; N, 18.09. Found: C, 69.87; H, 5.15; N, 18.12. General procedure for the 1,3-dipolar cycloaddition of quinazoline (**15**) and chlorophenylhydrazones **2a,c,d**. Triethylamine 1.35 mL (10 mmol) was added to a solution of quinazoline (5 mmol, 0.65 g) and chlorophenylhydrazones (5 mmol) in anhydrous tetrahydrofuran (20 mL). The mixture was stirred at room temperature for an appropriate time (**2a**, 72 h; **2b**, 24 h; **2c**, 48 h). The chlorohydrate of triethylamine was removed by filtration. The solution was evaporated under reduced pressure and the residue crystallized from ethanol. In the reaction with **2a** the solid obtained was 3-carbomethoxy-1-phenyl-1,10b-dihydro[1,2,4]triazolo[4,3-*c*]quinazoline (**17a**): yield 33%; mp 158–160 °C; IR cm^{-1} 1720 (C=O), 1610 (C=N); ^1H NMR: δ 3.93 (s, 3H, CH₃), 6.36 (s, 1H, H-10b), 7.05–7.45 (m, 9H, Ar-H), 8.37 (s, 1H, H-5); ^{13}C NMR: δ 53.1 (q), 74.0 (d), 115.5 (d), 120.9 (s), 134.5 (s), 123.2 (d), 124.0 (d), 124.6 (d), 126.9 (d), 129.5 (d), 129.2 (d), 138.6 (d), 139.4 (s), 143.6 (s), 157.9 (s). Anal. Calcd for C₁₇H₁₄N₄O₂: C, 66.66; H, 4.61; N, 18.29. Found: C, 66.76; H, 4.64; N, 18.31. The solution was concentrated to afford 1-carbomethoxy-3-phenyl-3,3a-dihydro[1,2,4]triazolo[4,3-*a*]quinazoline (**16a**): yield 20%; mp 152–154 °C; IR cm^{-1} 1715 (C=O), 1620 (C=N); ^1H NMR: δ 3.89

(s, 3H, CH₃), 6.75 (s, 1H, H-3a), 7.00 (t, 1H, *p*-C₆H₅, $J = 7.1$ Hz), 7.24–7.45 (m, 6H, H-6, H-7, Ar-H), 7.49 (m, 1H, H-8), 7.76 (m, 1H, H-9), 8.17 (s, 1H, H-5); ^{13}C NMR: δ 52.6 (q), 89.0 (d), 114.5 (d), 121.4 (d), 121.9 (s), 134.0 (s), 123.8 (d), 124.9 (d), 127.3 (d), 131.6 (d), 129.1 (d), 139.3 (s), 141.0 (s), 155.7 (d), 158.6 (s). Anal. Calcd for C₁₇H₁₄N₄O₂: C, 66.66; H, 4.61; N, 18.29. Found: C, 64.66; H, 4.63; N, 18.32. In the reaction with **2c** the solid obtained was 1-acetyl-3-phenyl-3,3a-dihydro[1,2,4]triazolo[4,3-*a*]quinazoline (**16c**): yield 32%; mp 138–140 °C; IR cm^{-1} 1670 (C=O), 1620 (C=N); ^1H NMR: δ 2.57 (s, 3H, CH₃), 6.70 (s, 1H, H-3a), 7.03 (t, 1H, *p*-C₆H₅, $J = 7.0$ Hz), 7.21 (t, 1H, H-7, $J = 7.5$ Hz), 7.30–7.55 (m, 6H, H-6, H-8, Ar-H), 7.81 (d, 1H, H-9, $J = 8.2$ Hz), 8.15 (s, 1H, H-5); ^{13}C NMR: δ 27.1 (q), 89.5 (d), 114.6 (d), 121.6 (s), 134.4 (s), 121.8 (d), 124.3 (d), 124.5 (d), 127.2 (d), 131.7 (d), 129.3 (d), 138.7 (s), 140.7 (s), 155.9 (d), 188.8 (s). Anal. Calcd for C₁₇H₁₄N₄O₂: C, 70.33; H, 4.86; N, 19.30. Found: C, 70.26; H, 4.83; N, 19.32. In the reaction with **2d**, the solid obtained was 1-benzoyl-3-phenyl-3,3a-dihydro[1,2,4]triazolo[4,3-*a*]quinazoline (**16d**): yield 32%; mp 150–153 °C; IR cm^{-1} 1640 (C=O), 1598 (C=N); ^1H NMR: δ 6.80 (s, 1H, H-3a), 7.03 (m, 1H, *p*-C₆H₅), 7.24 (m, 1H, H-7), 7.30–7.55 (m, 8H, H-6, H-8, Ar-H), 7.62 (m, 1H, *p*-COC₆H₅), 7.69 (d, 1H, H-9, $J = 8.2$ Hz), 8.15 (d, 2H, *o*-COC₆H₅, $J = 8.0$ Hz), 8.23 (s, 1H, H-5); ^{13}C NMR: δ 88.8 (d), 114.7 (d), 121.6 (s), 134.7 (s), 121.8 (d), 123.4 (d), 124.5 (d), 127.5 (d), 131.9 (d), 128.1 (d), 129.3 (d), 130.4 (d), 133.2 (d), 136.6 (s), 141.0 (s), 141.1 (s), 156.1 (d), 181.7 (s). Anal. Calcd for C₂₂H₁₆N₄O: C, 74.98; H, 4.58; N, 15.90. Found: C, 74.95; H, 4.56; N, 16.01.

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