A Facile Approach to 4,5-Dihydro[1,2,4]triazolo[3,2-d][1,5]benzoazepines

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Abstract: The novel tricyclic heterocycles of 4,5-dihydro[1,2,4]triazolo[3,2-d][1,5]benzoazepine derivatives were prepared by the cycloaddition of the corresponding bicyclic cationic 1,3-dipoles, which were easily generated from the azoacetates by reaction with AlCl₃ as a Lewis acid, to the triple bond of nitriles along with the consecutive ring expansion. The formation of products deviating from the normal reaction aptitudes was observed and the mechanistic aspects are discussed herein. Crystal diffraction analysis for two of the products unequivocally established the respective structures proposed.

Key words: 1-aza-2-azoniaallene cations, cycloaddition, nitriles, ring enlargement, benzoazepine

Benzoheteroazepine derivatives make up a broad class of heterocycles that has drawn much attention during the past few years because of its wide range of biological activities. In general, the attachment of a third heterocyclic ring to the seven-membered ring may enhance the activity or modify the activity profile.

In connection with our interests on the preparation of triazolo-fused azepine compounds, we have successfully synthesized a range of novel [1,2,4]triazolo-fused tricyclic heterocycles. The synthetic genre shares a common mechanistic agenda: the initial 1,3-dipolar cycloaddition of the in situ generated bicyclic carbenium ions from the α-chloroazo compounds with a Lewis acid at low temperatures with nitriles followed by a 1,2-aryl shift. Quite recently we also reported the synthesis of two new classes of heterocyclic systems, namely furo[3,2-c][1,2,4]triazolo[1,5-α]azepine and furao[2,3-f][1,2,4]triazolo[1,5-α]azepine. In line with this latter work, we found that the indispensable α-chloroazo compounds were not easily obtained in pure form and the usual approach suffered from unacceptable yields of the desired products and the number of reported substitution patterns was limited.

In this paper, aiming at achieving structural diversity, we describe the efficient synthesis of novel 4,5-dihydro[1,2,4]triazolo[3,2-d][1,5]benzoazepines by exploiting the cationic [3+2] cycloaddition reactions between 1-azao-2-azoniaallenum ions with nitriles using the bicyclic α-acetoxy azo compounds 3 as the key starting material.

The ethoxycarbonyl hydrazone 2a-c were firstly prepared by condensation of the appropriate chroman-4-ones 1a-c with ethyl carbazate in refluxing ethanol in the presence of a catalytic amount of acetic acid. Treatment 2 with 1.5 equivalents of lead tetraacetate in ice-cooled dichloromethane produced the α-acetoxy azo compounds 3a-c in moderate to high yields (Scheme 1). For the synthesis of the target heterocycles, the well-documented procedure from this laboratory was applied.

Thus, reacting the α-acetoxy azo compounds 3 with AlCl₃ at low temperature (−60 °C) in anhydrous CH₂Cl₂ provides, upon departure of the acetoxy group, the bicyclic 1-aza-2-azoniaallenum salts 4. Intermediates 4 are generally highly reactive and unstable, but can behave as a kind of positively charged 1,3-dipoles. In the presence of a nitrile, 4 can be captured to produce the 3-spiro-substituted 3H-1,2,4-triazolium salts 5. On elevating the temperature to above the room temperature (~30 °C), ring enlargement via a 1,2-shift occurs leading to the formation of the triazolobenzoazepinium trichloroacetoxylate aluminates 6. Basic treatment of 6 affords the 4,5-dihydro[1,2,4]triazolo[3,2-d][1,5]benzoazepine derivatives 7 (Scheme 2).

Based on the above protocol, substrates 3a-c were allowed to react with different kinds of nitriles and the results are listed in Table 1. If 3a was employed as the substrate, the reaction with acetonitrile provided the 4,5-dihydro[1,2,4]triazolo[3,2-d][1,5]benzoazepine 7a in 82% yield (Table 1, entry 1). Similarly, the reaction with butyronitrile gave 7b in comparable yield (Table 1, entry 2). To test the scope of the reaction, an aromatic nitrile, benzonitrile, was employed. However, under our standard
conditions, considerable decomposition of the product was observed and the attempt to isolate the corresponding tricyclic compound 7c was unsuccessful (Table 1, entry 3).

We then switched to benzyl cyanide following the reaction sequence as described above. Unexpectedly, the 1H NMR spectrum of the crude products showed clearly a doublet signal at 7.78 ppm with $J = 16.0$ Hz at the expense of the signal at about 5.3 ppm due to the methine proton connected to the phenyl group. After several chromatographic purifications, a white solid was obtained which was proved to be the 5-styryl-substituted 1H-1,2,4-triazole 8 by careful analysis of NMR and IR spectra (Table 1, entry 4).

It is known that the conjugate Michael addition reaction is an equilibrium process and a driving force is usually required to favor the formation of addition products. Furthermore, the base need be present only as a catalyst. In our case, NaOH was employed as a substrate in order to hydrolytically remove the N(1)-ethoxycarbonyl group. Because the methylene protons connected to the triazolo ring is much acidic, 7d may undergo NaOH-mediated deprotonation giving out the carbanion I. Fission of the phenoxy–carbon bond driven by formation of the more stable phenoxy anion II and intermolecular proton transfer may occur to afford the isolated 1H-1,2,4-triazole 8 (Scheme 3).

Based on the above consideration, we performed the final hydrolysis using sodium bicarbonate as base in order to diminish the retro-Michael-type ring opening of the oxazepine ring. However, compound 8 was still obtained as the major product, even if the hydrolysis was carried on at very lower temperatures (down to $-60^\circ$C). The usual 6-7-5 tricyclic compound 7d could only be detected in tiny

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\text{Scheme 2} \quad \text{Reaction of 3 with nitriles in the presence of } \text{AlCl}_3. \text{Reagents and conditions:} \ (i) \ \text{AlCl}_3, \ \text{CH}_2\text{Cl}_2, -70 \text{ to } -60 \ ^\circ \text{C}; \ (ii) \ R^5\text{CN}, -60 \ ^\circ \text{C}, \ 2 \ h; \ (iii) \ 30 \ ^\circ \text{C}, \ 1 \ h; \ (iv) \ \text{aq NaOH}, \ 0 \ ^\circ \text{C}, \ 20 \ \text{min.}
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\text{Scheme 3} \quad \text{A plausible mechanistic rationalization for the formation of the 5-styryl-substituted 1H-1,2,4-triazole 8}
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amount from the NMR of the crude product. The structure 8 was ascertained by the X-ray diffraction analysis.

During the investigation with 3b as the substrate, inferior results were obtained as compared with 3a. Thus, following the general protocol the reaction with acetonitrile proceeded well leading to the formation of 7g in moderate yield (Table 1, entry 5). However, the use of benzonitrile as well as benzyl cyanide resulted in the formation of 7f, 7i, 7j, 7k, 7l, 7g, 7h, 7c, 7b, 7a, 9a, and 9b, which was contaminated by decomposed products. Separation of these.
for the methine proton of compounds 7a–c and 7g were located at about 5.3 ppm, suggesting that the seven-membered ring has a rigid conformation making the two adjacent methylenic protons which are connected to the triazolo ring have a rigid conformation making the two adjacent protons located at about 5.3 ppm, suggesting that the seven-membered ring to these CH2 protons were found between 3.0–3.5 ppm which are very characteristic for an aryl migration. Otherwise, the respective signals of the products 7’ (Figure 1), formed by aliphatic side migration, would be found significantly downfield. The structure was further confirmed by an X-ray analysis for 7a.

Figure 1 Structure of 7’

In summary, we have reported here a facile approach to 4,5-dihydro[1,2,4]triazolo[3,2-d][1,5]benzoxazepines 7 by feasible cycloaddition of the in situ generated bicyclic azocarbenium ions 5 to nitriles along with a complete re-aromatization. The formation of the ring-opened product 8 and the two products 10a and 10b demonstrated that anomalies could occur in certain cases.

Melting points are uncorrected. The IR spectra were recorded on a Jasco FT-IR spectrometer. The NMR spectra were obtained using a JEOL ECA 400 with TMS as internal standard and are reported in δ units. Coupling constants (J) were provided in Hz. Mass spectra and high-resolution mass spectra were measured on a Finnigan MAT. X-ray diffraction analysis of 7a and 8 were measured with a Rigaku AFC7R diffractometer. All reagents were purchased from commercial sources and employed without further treatment. All solvents were purified and dried by standard methods prior to use. Chroman-4-ones 1a–c were prepared using the literature methods.12,13

Hydrazones: 2nd General Procedure
A mixture of the chroman-4-one 1 (10 mmol) and ethyl carbazate (1.25 g, 12 mmol) containing a few drops of glacial AcOH were refluxed in EtOH for 4 h. After cooling, the precipitate was collected by filtration to provide the hydrazone 2 as a white solid, which was sufficiently pure for the next synthetic step.

6-Methyl-2-phenylchroman-4-one (Ethoxycarbonyl)hydrazone (2a)
Yield: 83%; white solid; mp 216–217°C.
IR (KBr): 700, 1332, 1424, 1495, 1694, 3232 cm−1.
1H NMR (CDCl3): δ = 1.32 (t, J = 6.9 Hz, 3 H, CH3), 2.25 (s, 3 H, CH3), 2.66 (dd, J = 12.4, 16.5 Hz, 1 H, OCHCH3), 2.97 (d, J = 15.1 Hz, 1 H, OCH2), 4.27 (q, J = 6.9 Hz, 2 H, OCH2), 5.08 (dd, J = 12.4, 3.2 Hz, 1 H, OCHCH3), 6.87 (d, J = 8.3 Hz, 1 H, aryl), 7.09 (d, J = 8.3 Hz, 1 H, aryl), 7.35–7.50 (m, 5 H, C6H5), 7.95 (s, 1 H, aryl).

6-Methoxy-2-phenylchroman-4-one (Ethoxycarbonyl)hydrazone (2b)
Yield: 68%; white solid; mp 200–202°C.
IR (KBr): 1081, 1332, 1424, 1495, 1694, 3232 cm−1.
1H NMR (CDCl3): δ = 1.33 (t, J = 6.9 Hz, 3 H, CH3), 2.66 (dd, J = 12.4, 16.5 Hz, 1 H, OCHCH3), 2.97 (dd, J = 16.5, 2.8 Hz, 1 H, OCHCH3), 3.84 (s, 3 H, OCH3), 4.28 (q, J = 6.9 Hz, 2 H, OCH2), 5.07 (dd, J = 12.4, 3.2 Hz, 1 H, OCHCH3), 6.90 (s, 2 H, aryl), 7.38–7.50 (m, 5 H, C6H5), 7.51 (s, 1 H, aryl), 7.75 (s, 1 H, NH).

5,7-Dimethylchroman-4-one (Ethoxycarbonyl)hydrazone (2c)
Yield: 96%; white solid; mp 130–132°C.
IR (KBr): 1076, 1310, 1380, 1424, 1484, 1619, 1701, 1923, 1979, 3234 cm−1.
1H NMR (CDCl3): δ = 1.34 (t, J = 6.9 Hz, 3 H, CH3), 2.26 (s, 3 H, CH3), 2.66 (s, 3 H, CH3), 2.70 (t, J = 6.4 Hz, 2 H, OCH2CH3), 4.19 (t, J = 6.4 Hz, 2 H, OCH2CH3), 4.29 (q, J = 6.9 Hz, 2 H, OCH2CH3), 6.56 (s, 1 H, aryl), 6.67 (s, 1 H, aryl), 7.82 (s, 1 H, NH).

4-Acetoxy-4(ethoxycarbonylazo)chromanes 3; General Procedure
A solution of hydrazone 2 (2 mmol) in CH2Cl2 (5 mL) was added dropwise to a cooled (0°C) solution of Pb(OAc)4 (1.33 g, 3 mmol) in CH2Cl2 (10 mL) under vigorous stirring. After addition, the mixture was gradually warmed to 25°C and stirred for an additional 1 h, then poured into ice-water (20 mL). The precipitates were removed by filtration and the organic layer was separated and washed sequentially by H2O and aq dilute NaHCO3 solution until free from AcOH. After drying (Na2SO4), the solvent was removed under reduced pressure to afford the crude oily product 3, which was purified by chromatography on silica gel using CH2Cl2 as eluent.

4-Acetoxy(ethoxycarbonylazo)-6-methyl-2-phenylchromane (3a)
Yield: 73%; yellow liquid.
IR (neat): 700, 820, 1052, 1121, 1231, 1368, 1498, 1618, 1766, 2927, 2983 cm−1.
1H NMR (CDCl3): δ = 1.42 (t, J = 7.3 Hz, 3 H, OCH2CH3), 2.19 (s, 3 H, CH3CO), 2.88 (s, 3 H, CH3), 3.00 (m, 2 H, OCH2CH3), 4.46 (q, J = 7.3 Hz, 2 H, OCH2CH3), 5.34 (m, 1 H, OCH2CH3), 6.90 (m, 1 H, aryl), 7.00 (s, 1 H, aryl), 7.14 (m, 1 H, aryl), 7.33–7.50 (m, 5 H, C6H5).

4-Acetoxy(ethoxycarbonylazo)-6-methoxy-2-phenylchromane (3b)
Yield: 75%; yellow liquid.
IR (neat): 698, 1052, 1223, 1368, 1497, 1690, 1766, 2961 cm−1.
1H NMR (CDCl3): δ = 1.41 (t, J = 7.3 Hz, 3 H, OCH2CH3), 2.19 (s, 3 H, CH3CO), 2.93–3.10 (m, 2 H, OCH2CH3), 3.75 (s, 3 H, OCH3), 4.46 (q, J = 7.3 Hz, 2 H, OCH2CH3), 5.34 (m, 1 H, OCH2CH3), 6.72 (m, 1 H, aryl), 6.94 (m, 2 H, aryl), 7.33–7.52 (m, 5 H, C6H5).

4-Acetoxy(ethoxycarbonylazo)-5,7-dimethylichromane (3c)
Yield: 91%; yellow liquid.
IR (neat): 737, 844, 1016, 1112, 1228, 1310, 1368, 1470, 1575, 1618, 1765, 2935, 2983 cm−1.
1H NMR (CDCl3): δ = 1.39 (t, J = 6.8 Hz, 3 H, CH3CH2O), 2.18 (s, 3 H, CH3), 2.23 (s, 6 H, 2 × CH3), 2.73–2.83 (m, 2 H, OCH2CH3), 4.20–4.25 (m, 2 H, OCH2CH3), 4.39–4.49 (m, 2 H, OCH2CH3), 6.58 (s, 2 H, aryl).
Reaction of 3 with Nitriles in the Presence of AlCl₃; General Procedure
A solution of AlCl₃ (0.53 g, 4 mmol) and an appropriate nitrile (1.5 mmol) in CH₂Cl₂ (10 mL) was cooled to −70 °C under N₂, and then a solution of compound 3 in CH₂Cl₂ (5 mL) was added slowly at this temperature. After stirring at −60 °C for 2 h, the mixture was allowed to warm to 30 °C and stirred for another hour. The mixture was cooled to 0 °C, and then aq 1 N NaOH was carefully added under vigorous stirring. This mixture was allowed to stir at this temperature for 30 min, and the resultant solution was extracted with CH₂Cl₂ (3 × 20 mL). The organic layers were combined and washed with H₂O (2 × 30 mL) and dried (Na₂SO₄). Removal of the solvent by vacuum evaporation afforded the crude oily product which was purified by chromatography on silica gel using petroleum ether (bp 60–90 °C) and EtOAc (3:1) as eluent to provide heterocycles 7, 8, or 10.

4,5-Dihydro-2,9-dimethyl-5-phenyl[1,2,4]triazolo[3,2-d][1,5]benzoazepine (7a)

Yield: 82%; white solid; mp 111–112 °C.

IR (KBr): 701, 747, 811, 1002, 1237, 1347, 1396, 1441, 1503, 1535, 1679, 1929, 3035, 3389 cm⁻¹.

1H NMR (CDCl₃): δ = 2.35 (s, 3 H, CH₃), 2.43 (s, 3 H, CH₃), 2.46 (s, 3 H, CH₃), 3.05 (t, J = 6.8 Hz, 2 H, OCH₂CH₃), 4.55 (t, J = 6.8 Hz, 2 H, OCH₂CH₃), 6.88 (s, 1 H, ary1), 6.95 (s, 1 H, ary1).

13C NMR (CDCl₃): δ = 160.0, 154.8 (C=N), 149.5, 139.1, 133.7, 128.5, 127.9, 121.0 (aryl), 75.4 (OCH₂), 25.24, 21.04, 18.80.


4,5-Dihydro-8,10-dimethyl-2-phenyl[1,2,4]triazolo[3,2-d][1,5]benzoazepine (7b)

Yield: 51%; white solid; mp 103–104 °C.

IR (KBr): 728, 1072, 1204, 1530, 1442, 1492, 1530, 1612, 2927 cm⁻¹.

1H NMR (CDCl₃): δ = 2.35 (s, 3 H, CH₃), 2.50 (s, 3 H, CH₃), 3.15 (t, J = 6.4 Hz, 2 H, OCH₂CH₃), 4.59 (t, J = 6.4 Hz, 2 H, OCH₂CH₃), 6.90 (s, 1 H, ary1), 6.97 (s, 1 H, ary1), 7.39–7.46 (m, 3 H, ary1), 8.17 (m, 2 H, ary1).

13C NMR (CDCl₃): δ = 161.2, 155.1 (C=N), 149.5, 139.4, 133.8, 130.9, 129.1, 128.6, 128.5, 127.9, 126.3, 121.1 (aryl), 75.2 (OCH₂), 25.24, 21.04, 18.80.

HRMS (ESI): m/z calcd for C₁²H₁₂N₂O₂ [M⁺]: 292.1450; found: 292.1446.

2-Benzyl-4,5-dihydro-8,10-dimethyl[1,2,4]triazolo[3,2-d][1,5]benzoazepine (7c)

Yield: 65%; white solid; mp 122–123 °C.

IR (KBr): 743, 855, 1369, 1509, 1526, 1611, 2922 cm⁻¹.

1H NMR (CDCl₃): δ = 2.32 (s, 3 H, CH₃), 2.52 (s, 3 H, CH₃), 3.02 (t, J = 6.4 Hz, 2 H, OCH₂CH₃), 4.12 (s, 2 H, PH₂CH₂), 4.51 (t, J = 6.4 Hz, 2 H, OCH₂CH₃), 6.88 (s, 1 H, ary1), 6.94 (s, 1 H, ary1), 7.20–7.38 (m, 5 H, C₆H₅).

13C NMR (CDCl₃): δ = 163.2, 154.8 (C=N), 149.4, 139.1, 133.8, 130.9, 128.4, 128.5, 128.4, 127.8, 126.3, 120.9 (aryl), 75.26 (OCH₂), 34.74, 25.12, 20.97, 18.67.

HRMS (ESI): m/z calcd for C₁²H₁₂N₂O₂ [M⁺]: 306.1606; found: 306.1602.

(6)-3-Benzyl-1-(2-hydroxy-5-methyl)phenyl-5-styryl-1H-1,2,4-triazole (8)

Yield: 56%; white solid; mp 152–153 °C.

IR (KBr): 691, 1291, 1422, 1514, 1639, 1365, 2922, 3432 cm⁻¹.

1H NMR (CDCl₃): δ = 2.33 (s, 3 H, CH₃), 4.10 (s, 2 H, CH₃), 6.82–7.48 (m, 14 H, ary1 and CH=CH), 7.78 (d, J = 16.0 Hz, 1 H, CH=CH), 8.31 (br, 1 H, OH).

13C NMR (CDCl₃): δ = 163.5, 154.0 (C=N), 148.99, 138.62, 137.6, 135.4, 131.4, 129.9, 129.5, 129.1, 128.9, 128.7, 127.5, 126.8, 126.3, 123.5, 118.6, 111.8 (aryl and CH=CH), 34.87, 20.55.

HRMS (ESI): Calcd for C₂₀H₁₉N₂O2 [M⁺]: 368.1763; found: 368.1738.

4,5-Dihydro-9-methyl-2-[4-(5-ethoxycarbonyl-2-methoxyphenox)phenyl]-5-phenyl[1,2,4]triazolo[3,2-d][1,5]benzoazepine (10a)

Yield: 74%; white solid; mp 140–141 °C.

IR (KBr): 816, 1021, 1129, 1231, 1264, 1501, 1601, 1708, 2225, 2926 cm⁻¹.


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