Tetrahedron Letters 49 (2008) 4099–4101

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: http://www.elsevier.com/locate/tetlet

Unprecedented base-promoted cascade transformation of a pyrimidinone derivative into a novel tricyclic bis-diazepinone

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ARTICLE INFO

Article history:
Received 16 March 2008
Revised 13 April 2008
Accepted 24 April 2008
Available online 27 April 2008

Keywords:
1,2,3,4-Tetrahydropyrimidin-2-ones
2,3,6,7-Tetrahydro-1*H*-1,3-diazepin-2-ones
Ring expansion
[1,3]Diazepino[1,7-*e*][1,3,5]triazocines

ABSTRACT

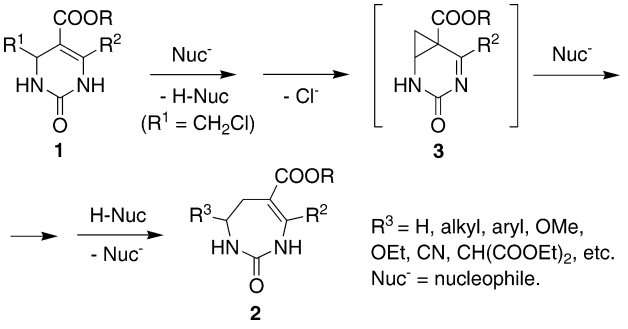
In the presence of strong bases (NaH, DBU, KOH), ethyl 4-chloromethyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, **4**, is transformed into a novel tricyclic compound, diethyl 9-methyl-5-methylene-3,11-dioxo-2,3,4,5,6a,7,10,11-octahydro-1,6-methano[1,3]diazepino[1,7-*e*][1,3,5]triazocine-6,8(1*H*)-dicarboxylate, **5**, as a result of a cascade reaction.

Biginelli compounds, **1**, are readily available heterocycles[1] with a wide range of biological activity (Scheme 1).[2] In contrast, their seven-membered analogs **2** are poorly accessible. Although several of these compounds have demonstrated promising antihypertensive action,[3] further studies of biological activity of compounds **2** are hindered by the lack of efficient methods for their preparation.

The only reported approach to diazepinones **2** consists of the treatment of **1** (R = Me, Et; $R^1 = CH_2Cl$; R^2 = Me, Ph) with nucleophilic agents such as $NaBH_4$, NaCN, sodium malonate, Grignard reagents, sodium succinimide, MeONa, and EtONa (Scheme 1).[3–7] The formation of diazepinones **2** was postulated to proceed via proton abstraction from N(1)H followed by intramolecular nucleophilic substitution at CH_2Cl to give a bicyclic intermediate **3** containing a cyclopropane ring.[5,6] Subsequent ring expansion in **3** led to diazepinones **2**. Summarizing their observations, the authors[5,6] concluded that the basic properties of the nucleophilic agent were important for the success of the reaction.

In our attempt to reveal the mechanistic details of this transformation, we studied the reaction of **1** with strong, non-nucleophilic bases without addition of nucleophilic agents using readily available pyrimidinone **4**[5,6] as a model compound.

When treated with NaH (1.1 equiv) in anhydrous MeCN at room temperature, compound **4** rapidly reacted to form, as evidenced by TLC, a single product **5** which was isolated after evaporation and aqueous work-up in 78% yield (Scheme 2).[8] Preliminary elucidation of the structure using ^1H and ^{13}C NMR[9] showed that compound **5** contained two ethoxycarbonyl groups, three NH groups of two urea fragments, a methyl group attached to a double bond, and an exocyclic methylene group and did not contain any chloromethyl groups. The number of carbon and hydrogen atoms equalled 18 and 24, respectively. The combustion analysis agreed with the molecular formula $C_{18}H_{24}N_4O_6$. This suggested the formation of a dimeric compound. Further detailed analysis of the ^1H and ^{13}C NMR spectra in DMSO-d_6, DMSO-d_6 + D_2O, and pyridine-d_5, and of ^1H,^1H-COSY, ^1H,^{13}C-HSQC, and ^1H,^{13}C-HMBC data allowed us to determine the structure of **5** as diethyl 9-methyl-5-methylene-3,11-dioxo-2,3,4,5,6a,7,10,11-octahydro-1,6-methano[1,3]diazepino[1,7-*e*][1,3,5]triazocine-6,8(1*H*)-dicarboxylate (Scheme 2). To the best of our knowledge, a tri-heterocyclic system of this type has never been described before.



Scheme 1. Synthesis of 2,3,6,7-tetrahydro-1*H*-1,3-diazepin-2-ones **2** by reaction of 4-chloromethyl substituted Biginelli compounds **1** with nucleophiles.

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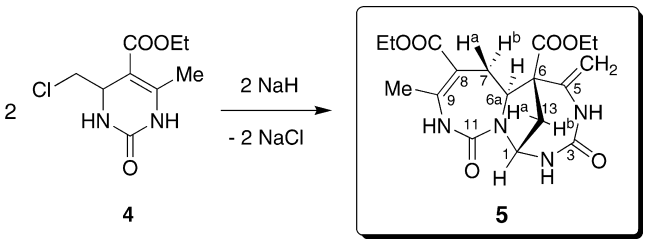
0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.04.136



Scheme 2. NaH-promoted diastereoselective transformation of **4** to [1,3]diazepino[1,7-*e*][1,3,5]triazocine **5**.

The specific features of the ^{1}H NMR spectra of **5** are the presence of a long range coupling constant $^5J_{7\text{-H(a)},9\text{-CH}_3} = 1.7$ Hz, which is typical for diazepinones **2**,[5,6] and the zero value of the vicinal constant $J_{1\text{-H},13\text{-H(b)}}$. The significant difference in the chemical shifts of the geminal protons 7-Hb and 7-Ha (0.83 ppm in DMSO-d_6 and 1.26 ppm in pyridine-d_5) was also noticeable and may be explained by the presence of the two neighboring anisotropic ethoxycarbonyl groups.

The ^{1}H and ^{13}C NMR data showed that compound **5** existed as a single diastereomer. Its relative configuration was determined by ^{1}H,^{1}H-NOESY experiments (Fig. 1).

For example, NOEs were observed between the 7-Ha and 13-Ha protons and between one of the hydrogens of the exocyclic methylene group and 6a-H. Calculations using semi-empirical methods AM1[10] showed that the distance between 6a-H and the nearest H in the methylene group in (1*R**,6*S**,6a*S**) and (1*R**,6*S**,6a*R**), the two possible diastereomers of **5**, equals 2.62 and 4.41 Å, respectively, and the distance between 7-Ha and 13-Ha equals 2.80 and 4.90 Å, respectively. Based on these data, the observed NOEs are only consistent with (1*R**,6*S**,6a*S**)-bis-diazepinone **5** (Scheme 2 and Fig. 2).

One possible explanation of the diastereoselective transformation of **4** to **5** is presented in Scheme 3. Similar to the mechanism in Scheme 1, a bicyclic compound **6** is believed to serve as a key intermediate. In the absence of other nucleophiles, **6** undergoes nucleophilic substitution with its own conjugated base **7** followed by ring expansion to give **8**. An intramolecular nucleophilic substitution/ring expansion in **8** forms the second diazepine cycle to give **9**. Finally, acylimine-enamide tautomerization and protonation leads to the tricyclic compound **5**.

We studied the influence of solvent, base, and molar ratio of the base with respect to **4** on the formation of **5**. In DMF, treatment of **4** with NaH (1.1 equiv) for 6 h at 20 °C resulted in smooth formation of **5** (79%). In less polar THF or 1,4-dioxane containing NaH (1.1 equiv), compound **5** was formed along with a considerable amount of side products. When the amount of NaH was reduced from 1.1 to 0.95 equiv (MeCN, 20 °C), extensive formation of side products was observed. With DBU (1.35 equiv) in MeCN (20 °C, 24 h), the product **5** was obtained in 59% yield. In the presence of KOH (1.1 equiv) in MeCN, dimerization of **4** to **5** proceeded with the formation of side products due to the strong nucleophilic nature of KOH. When **4** was treated with weaker bases (DABCO or *i*-Pr$_2$NEt) in MeCN, only the starting material was recovered

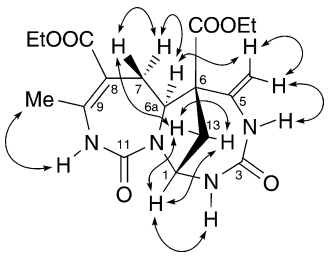


Figure 1. Diagnostic NOE relationships in **5**.

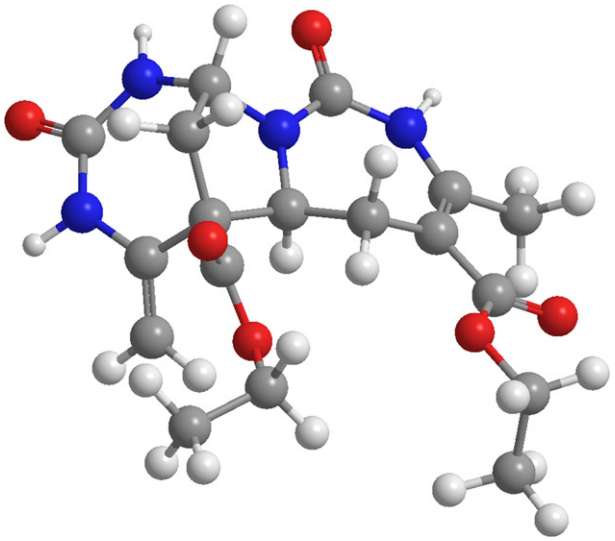
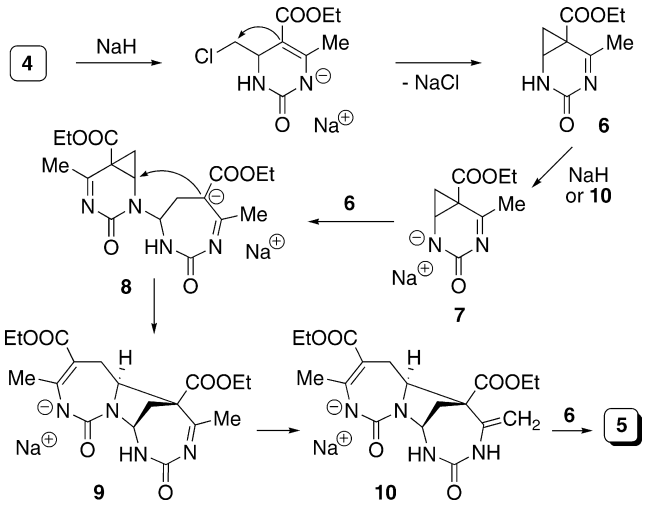


Figure 2. Geometry of **5** according to AM1 semi-empirical calculations.



Scheme 3. A plausible pathway for the transformation of **4** to **5**.

from the reaction mixture. The observations described above are in good agreement with the mechanism proposed in Scheme 3.

To confirm the proposed mechanism, detection of the intermediates **6**–**10** was attempted using ^{1}H NMR.[11] A solution of **4** in DMSO-d_6 was treated with NaH in an NMR tube and the progress of the reaction was monitored by ^{1}H NMR. However, the NMR spectra only showed the gradual transformation of **4** into **5**, which was complete in 30 min. No intermediates were detected in the reaction mixture at any point, presumably because of their short lifetimes.

In conclusion, we have found that, under anhydrous basic conditions, the fate of Biginelli compound depends strongly on the nucleophilicity and the polarity of the reaction medium. While in the presence of strong external nucleophiles compounds **2** are formed,[3–7] exposure of **4** to strong non-nucleophilic bases results in a cascade transformation leading to the diastereoselective formation of the novel bis-diazepinone **5**.

Acknowledgments

We thank Dr. Andrei Guzaev (AM Chemicals LLC, Oceanside, CA, USA) and Dr. Vyacheslav Samoshin (University of the Pacific, Stockton, CA, USA) for helpful discussions.

Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra and 2-D NMR spectra (^{1}H,^{1}H-COSY, ^{1}H,^{13}C-HSQC, ^{1}H,^{13}C-HMBC, ^{1}H,^{1}H-NOESY) for compound **5** in DMSO-d_6 and pyridine-d_5) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.04.136.

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8. Preparation of **5**: To a mixture of NaH (0.040 g, 1.68 mmol) and pyrimidine **4** (0.356 g, 1.53 mmol), anhydrous MeCN (7 mL) was added. Evolution of gas and formation of a pale yellow precipitate were observed. The reaction mixture was stirred for 7.5 h at rt and then evaporated in vacuo. The solid residue was treated with ice-cold water (3 mL), and the resulting suspension was acidified to pH 3 with aqueous HCl (4%). The mixture was cooled to 0 °C, the precipitate was filtered off, washed with cold water, and dried to give 0.234 g (78%) of compound **5** which was homogeneous by TLC, mp 244.5–245 °C (decomp., EtOH). Calcd for $C_{18}H_{24}N_4O_6$: C, 55.10; H, 6.16; N, 14.28. Found: C, 54.95; H, 6.25; N, 13.98.
9. Spectral characteristics of compound **5**: ^{1}H NMR (600.13 MHz, DMSO-d_6) δ: 8.48 (1H, s, N(10)-H), 8.31 (1H, dd, $^4J_{N(4)H,N(2)H}$ = 2.2, $^4J_{N(4)H,5\text{-}CH(a)}$ = 0.6 Hz, N(4)-H), 7.32 (1H, dd, $^3J_{N(2)H,1\text{-}H}$ = 6.6, $^4J_{N(2)H,N(4)H}$ = 2.2 Hz, N(2)-H), 4.99 (1H, dd, $^3J_{1\text{-}H,13\text{-}H(a)}$ = 7.2, $^3J_{1\text{-}H,N(2)H}$ = 6.6 Hz, 1-H), 4.82 (1H, d, $^2J_{5\text{-}CH(b),5\text{-}CH(a)}$ = 1.0 Hz, H(b) in 5-CH_2), 4.56 (1H, dd, $^2J_{5\text{-}CH(a),5\text{-}CH(b)}$ = 1.0, $^4J_{5\text{-}CH(a),N(4)H}$ = 0.6 Hz, H(a) in 5-CH_2), 4.22 (1H, $^2J_{CH(a),CH(b)}$ = 10.8, $^3J_{CH(a),CH_3}$ = 7.1 Hz, A part of ABX_3 spin system, OCH(a) in 6-COOEt), 4.18 (1H, $^2J_{CH(b),CH(a)}$ = 10.8, $^3J_{CH(b),CH_3}$ = 7.1 Hz, B part of ABX_3 spin system, OCH(b) in 6-COOEt), 4.05 (2H, q, $^3J_{CH_2,CH_3}$ = 7.1 Hz, OCH_2 in 8-COOEt), 3.77 (1H, dd, $^3J_{6a\text{-}H,7\text{-}H(a)}$ = 9.7, $^3J_{6a\text{-}H,7\text{-}H(b)}$ = 1.0 Hz, X part of A_3BMX spin system, 6a-H), 2.99 (1H, dd, $^2J_{7\text{-}H(b),7\text{-}H(a)}$ = 16.0, $^3J_{7\text{-}H(b),6a\text{-}H}$ = 1.0 Hz, M part of A_3BMX spin system, 7-H(b)), 2.58 (1H, dd, $^2J_{13\text{-}H(a),13\text{-}H(b)}$ = 13.1, $^3J_{13\text{-}H(a),1\text{-}H}$ = 7.2 Hz, 13-H(a)), 2.16 (1H, $^2J_{7\text{-}H(a),7\text{-}H(b)}$ = 16.0, $^3J_{7\text{-}H(a),6a\text{-}H}$ = 9.7, $^5J_{7\text{-}H(a),9\text{-}CH_3}$ = 1.7 Hz, B part of A_3BMX spin system, 7-H(a)), 2.16 (3H, d, $^5J_{9\text{-}CH_3,7\text{-}H(a)}$ = 1.7 Hz, A_3 part of A_3BMX spin system, 9-CH_3), 2.02 (1H, d, $^2J_{13\text{-}H(b),13\text{-}H(a)}$ = 13.1 Hz, 13-H(b)), 1.24 (3H, t, $^3J_{CH_2,CH_3}$ = 7.1 Hz, CH_3 in 6-COOEt), 1.18 ppm (3H, t, $^3J_{CH_2,CH_3}$ = 7.1 Hz, CH_3 in 8-COOEt). ^{13}C NMR (150.91 MHz, DMSO-d_6) δ: 170.18 (C=O in 6-COOEt), 167.84 (C=O in 8-COOEt), 156.47 (C3), 152.95 (C11), 145.05 (C9), 144.66 (C5), 104.11 (C8), 101.93 (=CH_2), 64.17 (C1), 63.49 (C6a), 61.31 (OCH_2 in 6-COOEt), 59.86 (C6), 59.53 (OCH_2 in 8-COOEt), 35.43 (C13), 32.48 (C7), 21.45 (9-CH_3), 14.12 (CH_3 in 8-COOEt), 13.65 ppm (CH_3 in 6-COOEt). IR (KBr) ν: 3225, 3106 (ν NH), 1731 (ν C=O in 6-COOEt), 1693, 1667, 1628 (ν C=O in 8-COOEt, ν C=C, amide-I), 1257, 1145, 1076 cm^{-1} (ν C–O).
10. Calculations were performed using the AM1 method using WinMopac 7.21 (http://www.psu.ru/science/soft/winmopac/index_e.html).
11. A solution of **4** (10.7 mg, 0.046 mmol) in DMSO-d_6 (0.5 mL) was added to a 5 mm NMR tube charged with NaH (1.2 mg, 0.050 mmol). The mixture obtained was shaken carefully until the evolution of gas ceased and the solid had dissolved. ^{1}H NMR spectra (Bruker DPX-300) were then recorded every 2 min.