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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 7977–7979

Studies on isocyanides. A facile synthesis of 4,5-dihydro-1,4-benzothiazepin-3(2*H*)-ones via post-condensation modifications of the Ugi reaction

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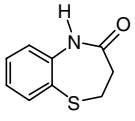
Received 30 August 2005; revised 12 September 2005; accepted 13 September 2005

Abstract—A series of 4,5-dihydro-1,4-benzothiazepin-3(2*H*)-ones **9** was prepared via Ugi 4-CC, S_N aliph, and S_N arom. This procedure, which resembles the well-known Hulme's and Zhu's protocols, allows a facile access to the above heterocyclic system. Further transformations of the cyclized products appear to be feasible.

Several derivatives of 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one[1] (**1**) have received considerable attention because of their pharmacological activities. Besides their use for the treatment of cardiovascular diseases,[2] some members of this class of compounds act as potent bradykinin agonists,[3] growth hormone secretagogues,[4] ligands for Src H2 protein,[5] spasmolytics,[6] and squalene synthetase inhibitors.[7]

Isomeric derivatives of 4,5-dihydro-1,4-benzothiazepin-3(2*H*)-one (**2**) are by far less known and, to the best of our knowledge, only one report dealing with their synthesis has appeared in the literature.[8]



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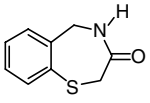

2

In continuation of our studies on the synthesis of heterocyclic compounds by isocyanide-based multi-component reactions,[9] we wish to report a viable synthesis of 4,5-dihydro-1,4-benzothiazepin-3(2*H*)-ones by exploiting the Ugi four-component condensation.[10] As the starting carbonyl component we chose the commercially available 2-chloro-5-nitrobenzaldehyde (**3**) in which the chlorine atom is readily displaced by nucleophiles. Aldehyde **3** reacted smoothly with amines **4**, isocyanides **5**, and chloroacetic acid (**6**) in methanol at room temperature to give the Ugi-4CC adducts **7** in fair to good yields.[11] Since both the chlorine atoms of **7** are reactive toward nucleophiles, in earlier experiments we attempted to promote the formation of an intramolecular sulfur bridge by reacting **7** with sulfides and hydrogen sulfides. Unfortunately, these attempts failed, giving intractable gums.

In an alternative approach, we attempted to achieve the formation of the sulfur bridge in two separate steps. The first step consisted of the reaction between **7** and thiourea. This reaction occurred very easily in acetone and compounds **7** were almost quantitatively converted into the corresponding isothiouronium salts **8**. In some reactions, salts **8** precipitated from the mother liquors in an almost pure form. However, the isolation of **8** was unnecessary and the following step could be performed on the crude product arising from the evaporation of the reaction mixture (Scheme 1).

Keywords: Ugi reaction; Isocyanides; 1,4-Benzothiazepinones; Aromatic nucleophilic substitution.
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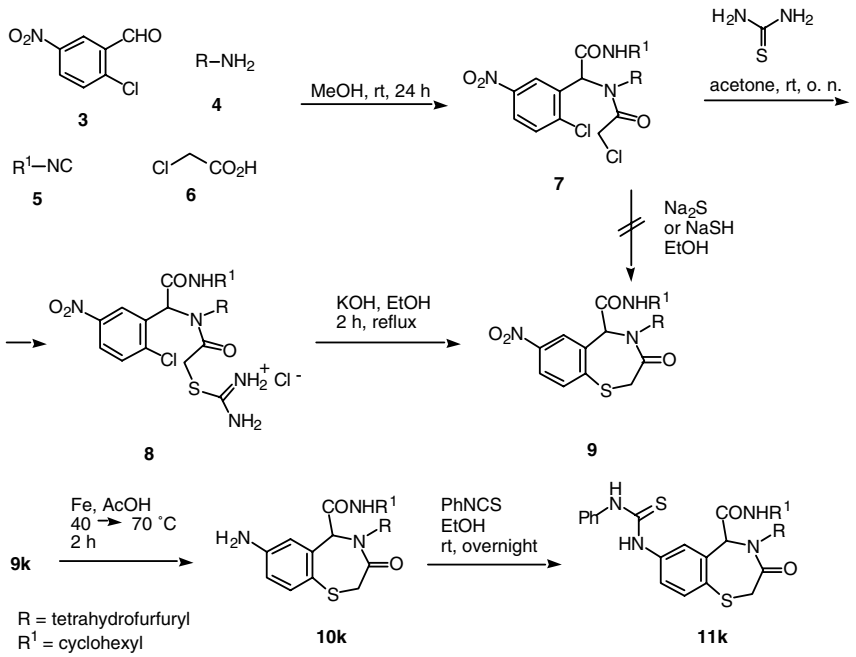
doi:10.1016/j.tetlet.2005.09.071



4	R
a	$C_6H_5CH_2$
b	4-$ClC_6H_4CH_2$
c	C_5H_5S [a]
d	$(CH_3)_2CHCH_2$
e	C_5H_9O [b]
f	3,4-$(OCH_2O)C_6H_3CH_2$
g	*n*-C_8H_{17}
h	4-$NO_2C_6H_4CH_2$

[a] 2-thienylmethyl; [b] tetrahydrofurfuryl

5	R^1
a	4-$C_2H_5OC_6H_4$
b	*c*-C_6H_{11}
c	*n*-C_6H_{13}

7,8,9	R	R^1	7 Yield (%)	9 Yield (%)[a]
a	$C_6H_5CH_2$	4-$C_2H_5OC_6H_4$	87	71
b	4-$ClC_6H_4CH_2$	4-$C_2H_5OC_6H_4$	65	95
c	C_5H_5S	4-$C_2H_5OC_6H_4$	72	67
d	$(CH_3)_2CHCH_2$	4-$C_2H_5OC_6H_4$	89	91
e	C_5H_9O	4-$C_2H_5OC_6H_4$	40	75
f	3,4-$(OCH_2O)C_6H_3CH_2$	*c*-C_6H_{11}	67	65
g	*n*-C_8H_{17}	4-$C_2H_5OC_6H_4$	82	40
h	4-$NO_2C_6H_4CH_2$	*c*-C_6H_{11}	72	60
i	C_5H_5S	*c*-C_6H_{11}	92	65
j	4-$ClC_6H_4CH_2$	*n*-C_6H_{13}	54	47
k	C_5H_9O	*c*-C_6H_{11}	72	62

[a] Based on **7**

Scheme 1. 4,5-Dihydro-1,4-benzothiazepin-3(2*H*)-ones via Ugi-4CC, aliphatic S_N, and aromatic S_N.

The cyclization of isothiouronium salts **8** took place successfully upon heating with 2 equiv of potassium hydroxide in ethanol to give the benzothiazepinones **9** in fair to excellent yields.[12,13]

In order to evaluate the possibility of obtaining derivatives of **9** via transformation of the nitro group, we performed the reduction of **9k** with iron powder in acetic acid.[9a,f] The crude amine **10k** was allowed to react with

phenyl isothiocyanate to give the thiourea **11k** in 65% overall yield.

In conclusion, the present method allows a facile preparation of derivatives containing the 1,4-benzothiazin-3-one core by means of a three-step synthesis. The first and the second steps are very easy to perform, simply by mixing the reagents. The purification of both the Ugi adducts **7** and the isothiouronium salts **8** is unnecessary and also the last step is experimentally simple. The final benzothiazinones are obtained in good yields and the substituents in position 4 and at the amide nitrogen can be easily changed by changing the amine and the isocyanide in the Ugi reaction. A further advantage lies in the possibility of transforming the nitro group in position 7.

Acknowledgments

A.G.N. is grateful to Junta de Extremadura for a research grant.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.09.071.

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11. *2-(N-Benzyl-N-chloroacetyl)amino-2-(2-chloro-5-nitro)phenylacetic acid N-(4-ethoxy)phenyl amide* (**7a**): A solution of 2-chloro-5-nitrobenzaldehyde (**3**) (1.11 g, 6.0 mmol) in MeOH (10 mL) was treated with benzylamine (**4a**) (642 mg, 6.0 mmol). The resulting mixture was stirred for 15 min at rt and then treated with a solution of the 4-ethoxyphenyl isocyanide (**5a**) (839 mg, 5.7 mmol) in MeOH (5 mL) and chloroacetic acid (**6**) (567 mg, 6.0 mmol), in the order given. The resulting mixture was stirred for 24 h at rt and then cooled and filtered. The collected product was washed with cold *i*-PrOH, *i*-Pr_2O, and pentane, in the order given, and dried to give 2.94 g (87%) of almost pure **7a**.
White solid; mp 177–178 °C (EtOH) IR (cm^{-1}): *v* 3251, 3078, 2979, 1679, 1653, 1612, 1531, 1511, 1476, 1466, 1411, 1346, 1304, 1244, 1204, 1167, 1117, 1049, 921, 836, 798, 742, 697, 521; ^1H NMR (200 MHz, $CDCl_3$): δ 8.50 (d, 1H, $J = 10.2$ Hz), 8.25 (dd, 1H, $J = 11.7$ Hz, $J = 2.4$ Hz), 7.34–7.06 (m, 9H), 6.76 (d, 2H, $J = 8.8$ Hz), 6.71 (d, 1H, $J = 11.2$ Hz), 4.91 (s, 2H), 4.18 (s, 2H), 3.98 (q, 2H, $J = 7.0$ Hz), 1.39 (t, 3H, $J = 6.8$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.62, 165.35, 156.11, 146.44, 142.01, 135.36, 133.94, 130.59, 129.96, 129.84, 128.71, 127.69, 125.73, 124.69, 121.98, 114.61, 63.75, 59.60, 59.44, 50.19, 41.96, 15.01. Anal. Calcd for $C_{25}H_{23}Cl_2N_3O_5$ (516.37): C, 58.15; H, 4.49; N, 8.14. Found: C, 58.37; H, 4.60; N, 7.86.
Detailed experimental procedures, physical, analytical, and spectral data of compounds **7b–k** are reported in the Supplementary data.
12. *4-Benzyl-7-nitro-3-oxo-2,3,4,5-tetrahydrobenzo[1,4]thiazepin-5-carboxylic acid N-(4-ethoxy)phenyl amide* (**9a**): A saturated solution of **7a** (1.55 g, 3.0 mmol) in acetone was treated with finely ground thiourea (297 mg, 3.9 mmol) and the resulting mixture stirred for 16 h at rt. TLC showed the absence of the starting product. Removal of the solvent left a residue, which was treated with EtOH (25 ml) and then with a solution of KOH (337 mg, 6.0 mmol) in water (2 mL). The resulting mixture was refluxed for 2 h under stirring. Removal of the solvent left a residue, which was stirred with water (60 mL). The resulting suspension was extracted with $CHCl_3$ (3×50 mL). The combined extracts were dried (Na_2SO_4) and the solvent removed to give a residue, which was recrystallized from EtOH to afford 1.43 g (71%) of pure **9a**.
White solid, mp 204.5–205.5 °C. IR (cm^{-1}): *v* 3323, 1697, 1659, 1595, 1572, 1520, 1469, 1427, 1415, 1336, 1308, 1264, 1230, 1172, 1156, 1113, 1083, 1061, 1036, 823, 758, 744, 702, 657; ^1H NMR (200 MHz, $CDCl_3$): δ 8.04 (d, 1H, $J = 8.7$ Hz), 7.84 (s, 1H), 7.48–7.35 (m, 6H), 7.03 (d, 2H, $J = 8.8$ Hz), 6.78 (s, 1H), 6.76 (d, 2H, $J = 8.8$ Hz), 5.31 (d, 1H, $J = 13.8$ Hz), 5.04 (s, 1H), 4.26 (d, 2H, $J = 15.0$ Hz), 3.96 (q, 2H, $J = 6.9$ Hz), 3.36 (d, 1H, $J = 14.5$ Hz), 1.37 (t, 3H, $J = 6.9$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.88, 156.40, 155.21, 144.68, 136.46, 129.81, 129.33, 129.21, 129.11, 128.90, 127.66, 123.43, 121.26, 114.79, 66.67, 63.69, 52.34, 33.07, 14.71.
Anal. Calcd for $C_{25}H_{23}N_3O_5S$ (477.53): C, 62.88; H, 4.85; N, 8.80. Found: C, 62.61; H, 4.96; N, 8.99. Detailed experimental procedures, physical, analytical, and spectral data of compounds **9b–k** are reported in the Supplementary data.
13. The formation of the internal nucleophile represents the key step in this synthesis. From this point of view the present methodology is substantially analogous to those described by Hulme and Zhu groups: (a) Tempest, P.; Ma, V.; Kelly, M. G.; Jones, W.; Hulme, C. *Tetrahedron Lett.* **2001**, *42*, 4963–4966; (b) Tempest, P.; Pettus, L.; Gore, V.; Hulme, C. *Tetrahedron Lett.* **2003**, *44*, 1947–1950; (c) Cristau, P.; Vors, J.-P.; Zhu, J. *Org. Lett.* **2001**, *3*, 4079–4082.