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# A facile synthesis of 1,4-benzodiazepine derivatives via Ugi four-component condensation

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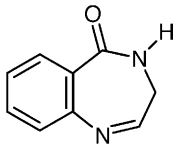
**Abstract**—A simple two-step route to 4,5-dihydro-3*H*-benzo[1,4]diazepin-5-ones is described. This synthesis, based on the isocyanide chemistry, allows a wide variety of substitution patterns starting from commercially available or easily obtainable reagents.


Among the various routes leading to the formation of 1,4-benzodiazepine derivatives, those based on the isocyanide multicomponent reactions are especially noteworthy. The key step of these methods is the Ugi four-component condensation[1] performed with anthranilic[2] or *N*-Boc protected anthranilic acids[3] and convertible isocyanides. Alternative syntheses are based on the use of bifunctional reagents such as ethyl glyoxylate,[4] α-amino acid esters,[5] *N*-Boc-1,2-diaminoethanes,[6] and *N*-Boc-α-aminoaldehydes.[7]

A careful examination of the literature shows that only a small number of derivatives of 4,5-dihydro-3*H*-1,4-benzodiazepin-5-one (**1**) bearing aryl groups in position 2 has been reported.[8]



**1**

Compounds arising from the reduction of the imine bond of derivatives of **1** showed anticonvulsive and central nervous system depressant activities.[9]

In a previous paper[10] we reported that phenacylamine can act as the amino component in the Ugi reaction, the low reactivity of aryl ketones in the conditions of the Passerini and Ugi reactions[11] preventing undesirable side-reactions.

Keeping in mind the above results we decided to attempt the synthesis of derivatives of **1** via the Ugi reaction by utilizing phenacylamine as the amine input.

The reaction between 5-chloro-2-nitrobenzoic acid (**2a**), potassium hydroxide, 4-methoxybenzaldehyde (**3a**), phenacylamine hydrochloride (**4a**), and cyclohexyl isocyanide (**5a**) proceeded smoothly in methanol at room temperature affording the desired adduct **6a** in 78% yield. The reduction of **6a** with iron powder in hot acetic acid gave the amino derivative **7a**, which could not be isolated since spontaneously cyclization to *N*-cyclohexyl 2-(7-chloro-4,5-dihydro-5-oxo-2-phenyl-3*H*-benzo-[1,4]diazepin-4-yl)-2-(4-methoxyphenyl)acetamide (**8a**) occurred in 76% yield.

The success of the experiment prompted us to verify the applicability of this synthesis by changing the components. In all of the cases studied the Ugi reaction proceeded smoothly in methanol at room temperature.[12] The Ugi 4-CC adducts **6a–d** arising from the acid **2a** and aromatic aldehydes were isolated by filtration in good yields and in almost pure form. The more soluble adducts **6e–j** were isolated by a simple work-up. The reductive cyclization of those compounds worked well and the benzodiazepines **8** were obtained in good overall yields.[13] The results are summarized in the Scheme 1.

*Keywords*: Ugi reaction; Isocyanides; 1,4-Benzodiazepines.
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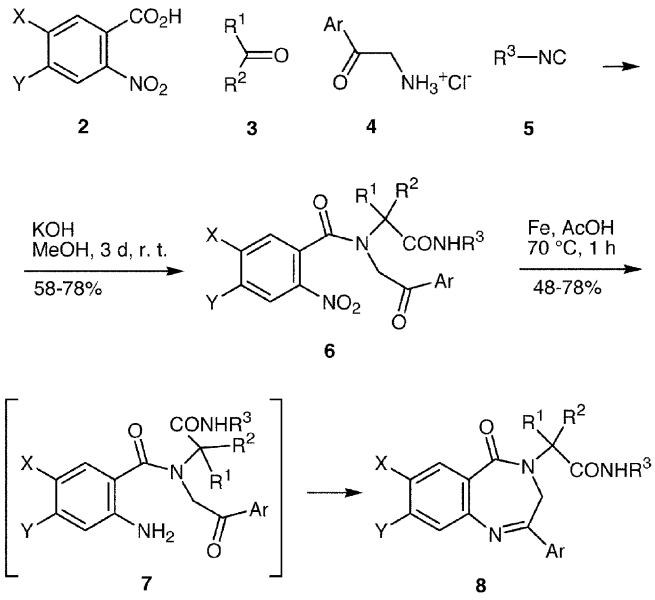


| 2 | X | Y |
|---|---|---|
| a | Cl | H |
| b | H | Cl |
| c | H | H |

| 3 | $R^1$ | $R^2$ |
|---|---|---|
| a | 4-$CH_3OC_6H_4$ | H |
| b | $C_6H_5$ | H |
| c | 4-$CH_3C_6H_4$ | H |
| d | 4-$ClC_6H_4$ | H |
| e | 2-$CH_3C_6H_4$ | H |
| f | *i*-$C_3H_7$ | H |
| g | *n*-$C_{11}H_{23}$ | H |
| h | –$CH_2$–$(CH_2)_2CH_2$– | |

| 4 | Ar |
|---|---|
| a | $C_6H_5$ |
| b | 4-$ClC_6H_4$ |

| 5 | $R^3$ |
|---|---|
| a | *c*-$C_6H_{11}$ |
| b | $C_6H_5CH_2$ |
| c | *n*-$C_6H_{13}$ |

| 6,7,8 | X | Y | $R^1$ | $R^2$ | Ar | $R^3$ | 6 Yield (%) | 8 Yield (%) |
|---|---|---|---|---|---|---|---|---|
| a | Cl | H | 4-$CH_3OC_6H_4$ | H | $C_6H_5$ | *c*-$C_6H_{11}$ | 78 | 76 |
| b | Cl | H | $C_6H_5$ | H | 4-$ClC_6H_4$ | *c*-$C_6H_{11}$ | 78 | 68 |
| c | Cl | H | 4-$CH_3C_6H_4$ | H | 4-$ClC_6H_4$ | *c*-$C_6H_{11}$ | 69 | 71 |
| d | Cl | H | 4-$ClC_6H_4$ | H | $C_6H_5$ | *c*-$C_6H_{11}$ | 76 | 78 |
| e | H | H | 2-$CH_3C_6H_4$ | H | $C_6H_5$ | *c*-$C_6H_{11}$ | 71 | 71 |
| f | H | H | *i*-$C_3H_7$ | H | $C_6H_5$ | $C_6H_5CH_2$ | 71 | 65 |
| g | Cl | H | *n*-$C_{11}H_{23}$ | H | $C_6H_5$ | *n*-$C_6H_{13}$ | 58 | 48 |
| h | Cl | H | –$CH_2$–$(CH_2)_2CH_2$– | | $C_6H_5$ | *c*-$C_6H_{11}$ | 68 | 69 |
| i | H | Cl | 4-$CH_3C_6H_4$ | H | $C_6H_5$ | *c*-$C_6H_{11}$ | 65 | 73 |
| j | H | Cl | 4-$ClC_6H_4$ | H | $C_6H_5$ | *c*-$C_6H_{11}$ | 69 | 77 |

**Scheme 1.** 2-Aryl-4,5-dihydro-3*H*-benzo[1,4]diazepin-5-ones via Ugi-4CC, nitro group reduction, intramolecular imine bond formation.

In conclusion, the present method allows a facile access to 2-aryl-4,5-dihydro-3*H*-benzo[1,4]diazepin-5-one derivatives. Furthermore, as a consequence of the intrinsic features of the multicomponent reactions, a wide variety of products can be prepared from simple reagents, which are commercially available or easily obtainable by known procedures. Another advantage of this two-step synthesis lies in the possibility of introducing a functional group (the *N*-substituted amide), in the substituent linked in position 4.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.11.083.

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12. *2-[N-Benzoylmethyl-N-(5-chloro-2-nitrobenzoyl)]amino-2-(4-methoxyphenyl)acetic acid N-cyclohexylamide* (**6a**): Finely powdered 5-chloro-2-nitrobenzoic acid (**2a**) (1.31 g, 6.5 mmol) was added to a well-stirred solution of potassium hydroxide (365 mg, 6.5 mmol) in MeOH (15 mL). Phenacylamine hydrochloride **4** (1.12 g, 6.5 mmol) was added to the above suspension at 5–10 °C and stirring was continued for 10 min. The resulting suspension was treated with 4-methoxybenzaldehyde (**3a**) (885 mg, 6.5 mmol) and then with cyclohexyl isocyanide (**5a**) (0.71 g, 6.5 mmol) in MeOH (7 mL). After 3 d stirring at rt the reaction mixture was cooled and filtered to give a solid product, which was washed with water and dried to give nearly pure **6a** (2.86 g, 78%) as a white solid. Mp 210–212 °C (EtOH). IR (KBr, $cm^{-1}$): *v* 3307, 2937, 2852, 1693, 1676, 1624, 1525, 1344; $^1H$ NMR (200 MHz, $CDCl_3$): *δ* 8.21–6.87 (m, 13H, $H_{Ar}$+NH), 5.27 (s, 1H, 2-H), 5.10 (d, 1H, *J* = 17.0 Hz, $H_a$ $COCH_2$), 3.91 (m, 1H, 1-H $_{cyclohexane}$), 3.78 (s, 3H, $OCH_3$), 3.75 (d, 1H, *J* = 17.0 Hz, $H_b$ $COCH_2$), 2.01–1.20 (m, $10H_{cyclohexane}$); $^{13}C$ NMR (50 MHz, $CDCl_3$): *δ* 197.38 (CO), 167.82 (CO), 159.96 (CO), 143.33, 141.66, 134.69, 134.33, 133.05, 131.51, 130.90, 130.70, 130.20, 129.41, 128.81, 128.65, 128.41, 127.58, 126.53, 125.91, 114.74, 114.31 ($C_{Ar}$), 66.77 (2C), 55.31 ($OCH_3$), 50.31 ($NCH_2$), 48.94 (CNH), 33.34, 33.17, 25.48, 25.10, 24.90 ($CH_2$).
Anal. Calcd for $C_{30}H_{30}ClN_3O_6$ (564.03): C, 63.88; H, 5.36; N, 7.45. Found: C, 63.99; H, 5.06; N, 7.35.
Detailed experimental procedures, physical, analytical, and spectral data of compounds **6b–j** are reported in the Supplementary data.
13. *2-(7-Chloro-4,5-dihydro-5-oxo-2-phenyl-3H-benzo[1,4]diazepine-4-yl)-N-cyclohexyl-2-(4-methoxyphenyl)acetamide* (**8a**): A solution of **6a** (3.10 g, 5.5 mmol) in AcOH (50 mL) was heated at 50 °C with the aid of a water bath. The bath was removed and when the temperature had dropped to 40 °C iron powder (Merck, 150 μm, 6.15 g, 110 mmol) was added in a single portion under vigorous stirring. When the slightly exothermic reaction had subsided, the reaction mixture was heated at 70 °C for 1 h. The resulting sludge was cooled and stirred with a mixture of water (150 mL) and chloroform (50 mL). After filtration through a Celite pad the phases were separated and the aqueous layer was extracted with chloroform (50 mL). The combined extracts were washed with water (30 mL), aq 5% $NaHCO_3$ (30 mL), water again (30 mL) and then dried ($Na_2SO_4$). Removal of the solvent under diminished pressure left an oily residue, which solidified upon stirring with *i*-$Pr_2O$. Filtration of this suspension gave almost pure **8a** (2.16 g, 76%) as a white solid. Mp 177–179 °C (EtOH). IR (KBr, $cm^{-1}$): *v* 3348, 2931, 2847, 1679, 1628, 1610, 729; $^1H$ NMR (200 MHz, $CDCl_3$): *δ* 8.03 (d, 1H, *J* = 2.6 Hz, 6-$H_{benzodiaz}$), 7.53 (dd, 1H, *J* = 7.8, 2.6 Hz, 8-$H_{benzodiaz}$), 7.34–7.04 (m, 8H, 9-$H_{benzodiaz}$ + $H_{Ar}$), 6.50 (d, 2H, *J* = 8.8 Hz, $H_{Ar}$), 6.29 (s, 1H, 2-H), 5.96 (d, 1H, *J* = 8.2 Hz, NH), 4.73 (d, 1H, *J* = 15.4 Hz, 3a-$H_{benzodiaz}$), 3.90–3.76 (m, 2H, 3b-$H_{benzodiaz}$ + 1-$H_{cyclohexane}$), 3.66 (s, 3H, $OCH_3$), 2.01–1.10 (m, $10H_{cyclohexane}$); $^{13}C$ NMR (50 MHz, $CDCl_3$): *δ* 168.27 (CO), 167.16 (CO), 166.56 (CN), 159.47, 145.19, 135.71, 131.87, 131.49, 130.74, 130.46, 130.41, 129.17, 128.06, 127.59, 127.43, 126.44, 114.04 ($C_{Ar}$), 60.43 (2-C), 54.97 ($OCH_3$), 48.74 (CNH) 41.46 (C-$3_{benzodiaz}$), 32.84, 32.73 25.40, 24.78, 24.71 ($CH_2$).
Anal. Calcd for $C_{30}H_{30}ClN_3O_3$ (516.03): C, 69.83; H, 5.86; N, 8.14. Found: C, 69.95; H, 5.88; N, 7.95.
Detailed experimental procedures, physical, analytical, and spectral data of compounds **8b–j** are reported in the Supplementary data.