Azide 1,3-Dipolar Cycloadditions to *N*-Propynoyl and *N*-Propenoyl (5*R*)-5-Phenylmorpholin-2-one: Diastereocontrolled Aziridine Formation

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Received 22 May 2008

Dedicated to Professor Sir Jack Baldwin FRS on the occasion of his 70th birthday

Abstract: *N*-Propynoyl (5*R*)-5-phenylmorpholin-2-one undergoes nonregioselective cycloaddition with aromatic azides to furnish mixtures of the corresponding triazoles, whereas *N*-propenoyl (5*R*)-5-phenylmorpholin-2-one reacts to furnish the corresponding diastereoisomerically pure aziridines in moderate to good yields, presumably via the intermediate triazolines.

Key words: (5*R*)-5-phenylmorpholin-2-one, triazole, triazoline, aziridine

In previous studies we have reported the application of the (5*R*)-5-phenylmorpholin-2-one template (**1**) to the synthesis of enantiomerically pure α-amino acids and enantiopure long-chain *threo*-2-amino-3-hydroxyesters using diastereocontrolled 1,3-dipolar cycloaddition of their azomethine ylid derivatives and alkylation chemistry on the 3,4-dehydro derivatives.[2]

1,3-Dipolar cycloaddition reaction of azides with dipolarophiles has resulted in a number of novel triazole and triazoline scaffolds which are useful for the creation of diverse chemical libraries.[3] In this letter we report the thermal 1,3-dipolar cycloaddition reactions of aromatic azides onto unsaturated amide derivatives **2** and **3** of (5*R*)-5-phenylmorpholin-2-one (**1**) and the unexpectedly ready extrusion of nitrogen from the triazoline adducts derived from **3**.

Synthesis of *N*-propynoyl (5*R*)-5-phenyl-4-morpholin-2-one (**2**) was readily achieved in 84% yield by condensation of **1** with propynoic acid using dicyclohexylcarbodiimide coupling and *N*-propenoyl (5*R*)-5-phenyl-4-morpholin-2-one (**3**) was prepared using propenoyl chloride–Et_3N in 78% yield (Scheme 1).[4]

In **3** the boat conformation of the heterocyclic ring, planar arrangement around the amide group and axial disposition of the C-5 phenyl substituent were demonstrated by single crystal X-ray diffraction analysis[5] and this disposition of the amide system is in keeping with previous observations (Figure 1).[6]

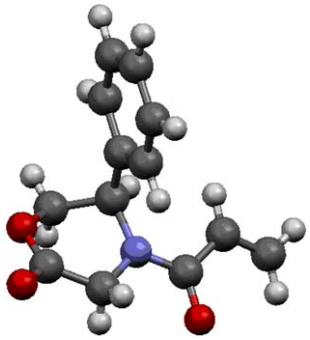
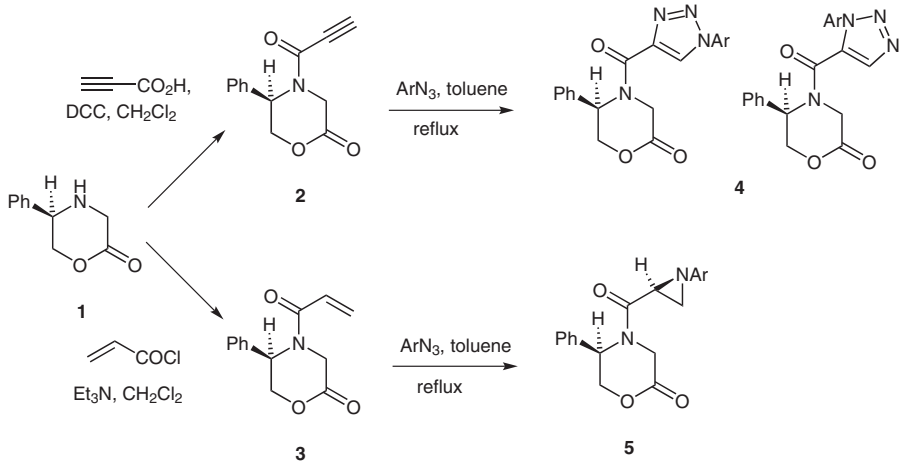


Figure 1 Single-crystal X-ray structure of propenamide **3**



Scheme 1

SYNLETT 2008, No. 14, pp 2119–2121
Advanced online publication: 15.07.2008
DOI: 10.1055/s-2008-1078595; Art ID: D17208ST

N-Propynoyl (5*R*)-5-phenylmorpholin-2-one (**2**) underwent ready 1,3-dipolar cycloaddition with a range of aromatic azides (prepared according to literature procedures[7]) in toluene at reflux. TLC monitoring showed that the morpholinone starting material was consumed within two to four hours, to afford the corresponding triazoles **4** in moderate to good yields as inseparable mixtures of regiosiomers in approximately equal proportions in each instance (Table 1).

However, when the propenamide derivative **3** was subjected to the same cycloaddition reactions the expected triazolines were not isolated but, instead, the aziridines **5** resulting from subsequent extrusion of nitrogen were obtained as single diastereoisomers in consistently good yields.[8] In all cases spectroscopic data were consistent with the structures assigned and, in addition the relative stereochemistry was assigned unambiguously by single crystal X-ray crystallographic analysis of **5a** (Figure 2).[5]

Such extrusion of nitrogen from triazolines has been observed previously, but the facility with which it occurs in this simple triazoline system was not expected, as it usually requires Brønsted acid or transition metal catalysis or specific structural features in the substrate.[9]

Table 1 Isolated Yields for Adducts **4** and **5**

Ar	**4**	Yield (%)	**5**	Yield (%)
Ph	**4a**	66	**5a**	67
4-MeC_6H_4	**4b**	44	**5b**	45
4-MeOC_6H_4	**4c**	38	**5c**	49
4-FC_6H_4	**4d**	41	**5d**	57
4-ClC_6H_4	**4e**	68	**5e**	77
4-BrC_6H_4	**4f**	50	**5f**	75
3-ClC_6H_4	**4g**	58	**5g**	78
3-BrC_6H_4	**4h**	62	**5h**	73
4-O_2NC_6H_4	**4i**	44	**5i**	66

The diastereocontrol is presumably a consequence of the axial phenyl substituent at C-5 of the morpholin-2-one ring and the hindered rotation around the amide bond.

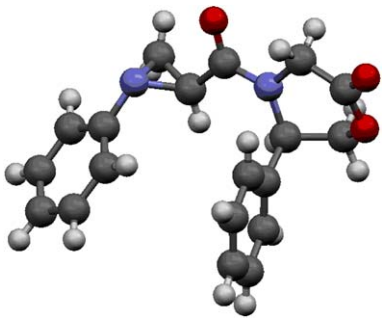


Figure 2 Single-crystal X-ray structure of aziridine adduct **5a**

As we were never able to isolate any triazolines arising from initial 1,3-dipolar cycloaddition with **3**, an alternative pathway involving diastereocontrolled Michael-type addition followed by elimination of nitrogen cannot be ruled out. For the same reason no conclusions can be drawn about any regiocontrol in the 1,3-dipolar cycloaddition if the triazolines **5** are intermediates. Nevertheless, the ease of isolation of the aziridines and the complete diastereocontrol in their formation is remarkable and unforeseen, permitting a synthetically useful means of generating sophisticated molecular architectures.

Acknowledgment

MD thanks the China Scholarship Council, Ministry of Education for financial support.

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(4) **Synthesis of *N*-Propynoyl (5*R*)-5-Phenylmorpholin-2-one (2)**: To a solution of (5*R*)-5-phenylmorpholin-2-one (0.53 g, 3 mmol) in anhyd CH_2Cl_2 (40 mL) was added propynoic acid (0.21 g, 3 mmol), and then dicyclohexylcarbodiimide (0.68 g, 3.3 mmol) in anhyd CH_2Cl_2 (10 mL) was added over 10 min. The resulting solution was stirred for 12 h. The solids were removed by filtration through a short pad of Celite® and washed with CH_2Cl_2 (10 mL). The solvent was removed under reduced pressure and the crude material was purified by flash column chromatography on silica, eluting with PE–EtOAc (3:1) to furnish the title compound as colourless needles (1.81 g, 84%); mp 125–126 °C; $[\alpha]_D^{20}$ –50.5 (*c* = 1.08, $CHCl_3$). IR (film): 3243, 1738, 1635 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.26–7.47 (m, 5 H), 5.60–5.66 (m, 1 H), 4.94 (d, *J* = 17.5 Hz, 0.5 H), 4.80

(d, J = 17.5 Hz, 0.5 H), 4.69–4.76 (m, 2 H), 4.33 (d, J = 17.5 Hz, 0.5 H), 4.16 (d, J = 17.5 Hz, 0.5 H), 3.29 (s, 0.5 H), 3.08 (s, 0.5 H). MS: m/z = 230 $[M + 1]^+$, 178, 148, 104, 99, 45.

Synthesis of *N*-Propenoyl (5*R*)-5-Phenylmorpholin-2-one (3): To a mixture of (5*R*)-5-phenylmorpholin-2-one (0.531 g, 3 mmol), Et_3N (9 mmol) and anhyd CH_2Cl_2 (40 mL), propenoyl chloride (0.408 g, 4.5 mmol) was added dropwise over 10 min. The resulting solution was stirred for 5 h under an atmosphere of nitrogen. The reaction was quenched by the addition of sat. Na_2CO_3 (40 mL), the aqueous phase was extracted with Et_2O (2 × 30 mL) and the combined extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude material was purified by flash column chromatography on silica, eluting with PE–Et_2O (1:5) to furnish the title compound as an oil. Crystallization from Et_2O produced colourless crystals (0.54 g 78%); mp 51–52 °C; $[\alpha]_D^{20}$ –69.9 (c = 4.65, $CHCl_3$). IR (film): 1747, 1651 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.28–7.51 (m, 7 H), 6.50 (m, 1 H), 6.01 (m, 1 H), 4.02–4.50 (m, 4 H). MS: m/z = 231, 178, 148, 104, 99, 45.

(5) X-ray data of **3**: $C_{13}H_{13}NO_3$, MW = 231.2; T = 293(3) K; monoclinic, $P2(1)$, a = 7.0336(1), b = 7.1121(6), c = 11.7883(7) Å; β = 91.464(7)°; Z = 2; D_x = 1.303 g·cm^{-3}; F(000) = 244; μ(Mo–K_α) = 0.093 mm^{-1}. The number of independent reflections used in the analysis was 1860 with $I \geq 2\sigma(I)$. Data were measured (θ_{max} = 30.13°) on an Oxford Diffraction Gemini S Ultra instrument using Mo–K_α radiation; final $R1$ = 3.12, $wR2$ = 7.78. **5a**: $C_{19}H_{18}N_2O_3$, M = 322.3; T = 293 (3) K; monoclinic, $P2(1)$, a = 7.2342(1), b = 11.7560(2), c = 9.9218(2) Å; β = 106.408(2)°; Z = 2; D_x = 1.321 g·cm^{-3}; F(000) = 340; μ(Cu–K_α) = 0.735 mm^{-1}. The number of independent reflections used in the analysis was 2107 with $I \geq 2\sigma(I)$. Data were measured (θ_{max} = 66.13°) on an Oxford Diffraction Gemini S Ultra instrument using CuK_α radiation; final $R1$ = 2.44, w$R2$ = 6.81. Atomic coordinates and further crystallographic details have been deposited at the Cambridge Crystallographic Data Centre, deposition numbers CCDC 689449 (**3**), CCDC 689448 (**5a**) and copies of these data can be obtained by applying to CCDC, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK; [fax: +44(1223)336033; email: deposit@ccdc.cam.ac.uk).

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(8) **Synthesis of Aziridine Adducts 5**: A solution of *N*-propenoyl (5*R*)-5-phenylmorpholin-2-one (**3**; 231 mg, 1 mmol) and the requisite aryl azide (1.5 mol) in toluene was heated to reflux for 2–3 h until TLC analysis indicated the absence of dipolarophile. Solvent was removed under reduced pressure and the crude material was purified by flash column chromatography on silica, eluting with PE–Et_2O (1:7) to furnish the compounds **5** as colourless solids. **Analytical Data for 5a**: mp 67–69 °C; $[\alpha]_D^{20}$ –112.7 (c = 1.0, $CHCl_3$). IR (film): 1762, 1663 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.10–7.50 (m, 5 H), 6.80–7.05 (m, 3 H), 6.20 (d, J = 7.5 Hz, 2 H), 5.35 (br t, J = 5.0 Hz, 1 H), 4.89 (d, J = 17.5 Hz, 1 H), 4.69 (dd, J = 11.0 Hz, J' = 3.0 Hz, 1 H), 4.35–4.60 (m, 2 H), 2.50–2.70 (m, 2 H), 2.10–2.25 (m, 1 H). MS: m/z = 323 $[M + 1]^+$, 178, 148, 104, 99, 45.

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