Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 5205–5208

Unexpected cleavage of the N–N bond in the reactions of 3-pyrazolidinone-1-azomethine imines with HCN

Lidija Pezdirc, Uroš Grošelj, Anton Meden, Branko Stanovnik and Jurij Svete*

Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, 1000 Ljubljana, Slovenia

Received 20 April 2007; revised 15 May 2007; accepted 24 May 2007
Available online 31 May 2007

Abstract—Treatment of (1*Z*,4*R**,5*R**)-1-arylmethylidene-4-benzamido-5-phenylpyrazolidin-3-one 1-azomethine imines **4a**–**d** with potassium cyanide in the presence of acetic acid resulted in addition of HCN to the exocyclic C=N double bond followed by β-eliminative N–N single bond cleavage (ring opening) to give the *N*-[(1*R**,2*R**)-3-amino-2-benzamido-3-oxo-1-phenylpropyl]benzimidoyl cyanides **6a**–**d** in 28–85% yields. Reaction of dipole **4e** with HCN furnished stable intermediate, (1′*S**,4*R**,5*R**)-4-benzamido-1-[cyano(mesityl)methyl]-5-phenylpyrazolidin-3-one (**5e**), in 76% yield. The structure of compound **6c** was determined by X-ray diffraction.

The importance of pyrazolidin-3-ones has increased significantly in the last decade, due to their applicability in industrial processes, and because several pyrazolidin-3-one derivatives exhibit biological activities. Some examples of important pyrazolidinone derivatives are given in Figure 1.[1–11]

Over the last decade, part of our research interest has also been devoted to the chemistry of pyrazolidinones and their fused analogs.[12–23] In connection with this, 5,5-dimethylpyrazolidin-3-one (**1**) and (4*R**,5*R**)-4-benzamido-5-phenylpyrazolidin-3-one (**2**) (cf. Fig. 1) were used as model compounds for further transformations into pyrazolylalanines,[13,14] β-alkylamino-β-phenylalaninamides,[15] pyrazolo[1,2-*a*]pyrazolones[12,18,21,23] and other functionalised heterocycles.[16,17,19] Our studies on the 3-pyrazolidinone series were focused on 1,3-dipolar cycloadditions of 3-pyrazolidinone-1-azomethine imines to various dipolarophiles in order to establish the reactivity and selectivity pattern of these reactions. Generally, these cycloadditions were highly stereoselective with stereocontrol depending on the structure of both components: the dipole and the dipolarophile.[18,21,23] Recently, these studies were also extended towards the combinatorial synthesis of pyrazolo[1,2-*a*]pyrazolones.[23]

Previously, we reported the reaction of (1*Z*,4*R**,5*R**)-1-benzylidene-4-benzamido-5-phenylpyrazolidin-3-on-1-azomethine imine (**4a**) with potassium cyanide in the presence of acetic acid.[12] On the basis of the spectral and analytical data of product **6a** and due to almost negligible C≡N absorption at ~2200 cm^{-1}, we concluded that 1,3-dipolar cycloaddition of **4a** to the C≡N triple bond took place to give a pyrazolo[1,2-*a*][1,2,3]triazole derivative.[12] Based on this example, we recently became interested in parallel cycloadditions of azomethine imines **4** to the C≡N triple bond. We expected that these reactions might offer access to pyrazolo[1,2-*a*][1,2,3]triazole derivatives and we carried out parallel reactions of azomethine imines **4a**–**e** with potassium cyanide in the presence of acetic acid. However, upon X-ray diffraction

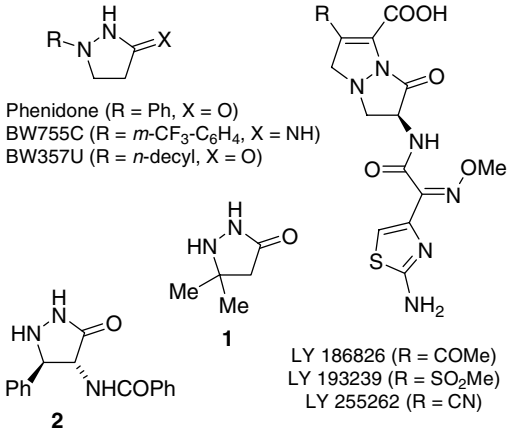


Figure 1. Some important pyrazolidinone derivatives.

* Corresponding author. Tel.: +386 1 2419 100; fax: +386 1 2419 220; e-mail: jurij.svete@fkkt.uni-lj.si

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.05.142

analysis of product **6c** (Fig. 2) we realised that cleavage of the N–N single bond (i.e., ring opening) had occurred and not the cycloaddition reaction. Thus, the previously published structural assignment for compound **6a** was erroneous,[12] as reaction of dipole **4a** with potassium cyanide gave *N*-[(1*R**,2*R**)-3-amino-2-benzamido-3-oxo-1-phenylpropyl]benzimidoyl cyanide (**6a**) and not the pyrazolo[1,2-*a*][1,2,3]triazole derivative. Herein, we report the preliminary results of a study on reactions of azomethine imines **4** with potassium cyanide.

First, (1*Z*,4*R**,5*R**)-1-arylmethylidene-4-benzamido-5-phenylpyrazolidin-3-on-1-azomethine imines **4a**–**e** were prepared by parallel acid-catalysed treatment of (4*R**,5*R**)-4-benzamido-5-phenylpyrazolidin-3-one (**2**) with aldehydes **3a**–**e** following the general literature procedure.[23] Dipoles **4a**–**e** were then treated with 1.5 equiv of potassium cyanide in the presence of 1.15 equiv of acetic acid in methanol at room temperature for 3 h to give products **6a**–**d** and **5e**, respectively, in 28–85% yields.[24–29] A possible explanation for the reaction mechanism includes addition of hydrogen cyanide to azomethine imine **4** giving adduct **5**. Subsequent β-elimination of the carboxamide moiety via N–N single bond fission (i.e., opening of the pyrazolidinone ring) leads to *N*-[(1*R**,2*R**)-3-amino-2-benzamido-3-oxo-1-phenylpropyl]benzimidoyl cyanide **6**. This proposed mechanism is supported by the isolation of intermediate **5e**, which did not undergo ring opening. The higher stability of **5e** might be explained by steric hindrance as a result of the two *ortho*-methyl groups, which prevent deprotonation and eliminative ring opening. An alternative explanation might be that the β-elimination step requires an antiperiplanar conformation around the C(1′)–N(1) single bond, which is not feasible in the case of a bulky mesityl group. Addition of HCN to the azomethine imine **4e** was stereoselective, since compound **5e** was isolated in diastereomerically pure form. Unfortunately, we were unable to determine the configuration at the newly formed stereocenter at position 1′. Presumably, addition of the cyanide to the exocyclic C(1′)=N(1) double bond took place preferentially from the less hindered *Re*-face to give the (1′*S**,4*R**,5*R**)-diastereoisomer **5e** (Scheme 1).

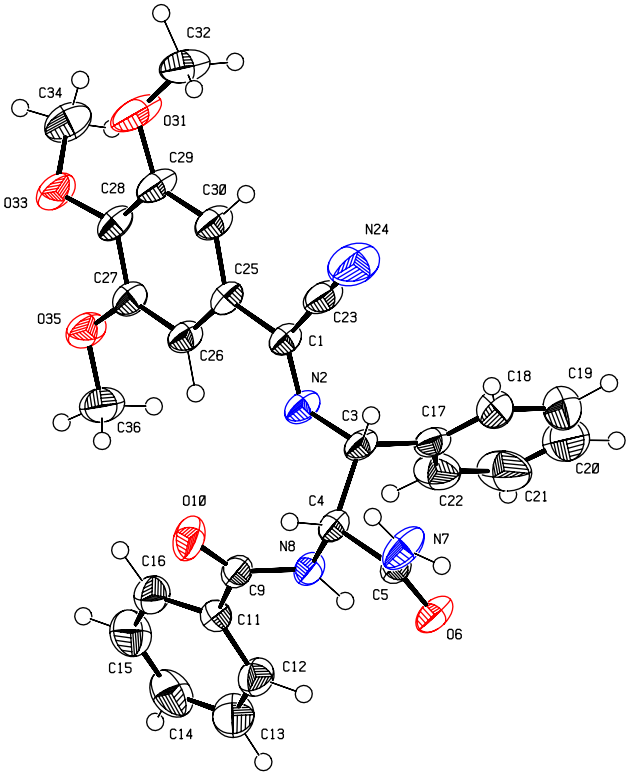
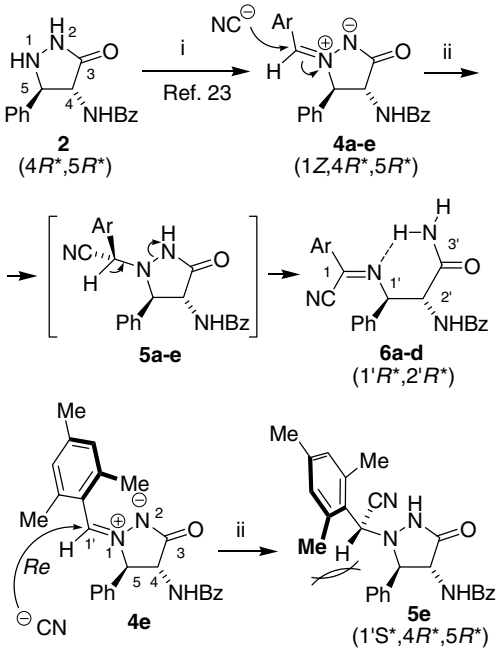


Figure 2. ORTEP view of compound **6c**.

The structures of compounds **6a**–**d** and **5e** were determined by spectroscopic (IR, ^{1}H NMR, ^{13}C NMR, MS, HRMS) methods and by analyses for C, H and N.[25–29] The structure of compound **6c** was determined by X-ray diffraction (Fig. 2).[30] The structures of **6a**, **b**, **d** were confirmed by correlation of the chemical shifts for the *H*–C(1′), *H*–C(2′) and NH_2 protons as well as by correlation of the $^3J_{H-H}$ coupling constants, $^3J_{H1'-H2'}$ and $^3J_{H2'-NH}$. In the ^{1}H NMR spectra of compounds **6a**–**d**, the $CONH_2$ group appeared as two singlets at ~7.1 ppm and ~7.6 ppm. This non-equivalency of NH_2 protons was not surprising and can be explained by the restricted rotation around the C–N single bond (topomerization),[31] enhanced by additional intramolecular C=N···H–N hydrogen bonding between the imine nitrogen atom and the amide protons (cf. Scheme 1). On the other hand, NMR data for compound **5e** were consistent with the 1-alkyl-3-pyrazolidinone structure. Simi-



Compound	Ar	Yield (%)
6a	phenyl	85
6b	4-methoxyphenyl	35
6c	3,4,5-trimethoxyphenyl	64
6d	2,6-dichlorophenyl	28
5e	2,4,6-trimethylphenyl	76

Scheme 1. Reagents and condition: (i) Ar–CHO (**3a**–**e**), EtOH, TFA (cat.), reflux (Ref. 23); (ii) KCN (1.5 equiv), AcOH (1.15 equiv), MeOH, rt.

Table 1. Selected ^{1}H NMR (300 MHz, DMSO-d_6) data for compounds **6a–d** and **5e**

Compound	δ (ppm)					$^3J_{H-H}$ (Hz)	
	1′-*H*	2′-*H*	N*H*Bz	$CONH_2$–H_a	$CONH_2$–H_b	1′–2′	NH–CH
6a	5.49	5.24	8.83	7.14	~7.6[a]	9.5	9.5
6b	5.44	5.20	8.81	7.11	7.61	9.4	9.4
6c	5.43	5.25	8.83	7.14	~7.6[a]	9.4	9.4
6d	5.64	5.25	8.83	7.17	7.57	9.5	9.5
	4-*H*	5-*H*	N*H*Bz	1′-*H*	2-*H*	4–5	NH–CH
5e	4.23	3.95	9.59	5.74	10.71	3.5	6.8

[a] Overlapped by other protons.

larly, the IR absorption at 1720 cm^{-1} in compound **5e** was in agreement with the typical vibration of the pyrazolidinone C=O group. Selected ^{1}H NMR data for compounds **6a–d** and **5e** are given in Table 1.

In conclusion, reactions of azomethine imines **4a–d** with in situ formed hydrogen cyanide unexpectedly led to β-eliminative N–N bond cleavage and furnished *N*-[(1*R**,2*R**)-3-amino-2-benzamido-3-oxo-1-phenylpropyl]-benzimidoyl cyanides **6a–d** as the reaction products. In addition to the previous examples,[15,17,32,33] this reaction represents a novel type of ring transformation reaction of pyrazolidine derived azomethine imines. To the best of our knowledge, this is also a rare example of N–N single bond fission, which takes place under essentially mild and non-reductive conditions. The proposed reaction mechanism is supported by the isolation of intermediate **5e**. Finally, this reaction could also offer access to *N*-(3-amino-3-oxopropyl)benzimidoyl cyanides as interesting intermediates for further transformations. Further investigation on the scope and limitations of this method is currently in progress.

Acknowledgements

The financial support from the Slovenian Research Agency through grants P0-0502-0103, P1-0179, and J1-6689-0103-04 is gratefully acknowledged. We thank the pharmaceutical companies Krka d.d. (Novo mesto, Slovenia) and Lek d.d., a Sandoz company (Ljubljana, Slovenia), and Boehringer Ingelheim Pharma GmbH & Co. KG (Biberach, Germany) for the financial support.

Crystallographic data were collected on a Kappa CCD Nonius diffractometer in the Laboratory of Inorganic Chemistry, Faculty of Chemistry and Chemical Technology, University of Ljubljana, Slovenia. We acknowledge with thanks the financial contribution of the Ministry of Science and Technology, Republic of Slovenia through grant Packet X-2000 and PS-511-102, which thus made the purchase of the apparatus possible.

References and notes

1. Dorn, H. *Chem. Heterocycl. Compd. U.S.S.R.* **1981**, 3–31, and references cited therein.
2. Claramunt, R. M.; Elguero, J. *Org. Proc. Prep. Int.* **1991**, *23*, 273–320, and references cited therein.
3. Elguero, J. In *Pyrazoles in Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier Science Ltd: Oxford, 1996; Vol. 3, pp 1–75, and references cited therein.
4. Jungheim, L. N.; Sigmund, S. K.; Fisher, J. W. *Tetrahedron Lett.* **1987**, *28*, 285–288.
5. Jungheim, L. N.; Sigmund, S. K. *J. Org. Chem.* **1987**, *52*, 4007–4013.
6. Indelicato, J. M.; Pasini, C. E. *J. Med. Chem.* **1988**, *31*, 1227–1230.
7. Ternansky, R. J.; Draheim, S. E. *Tetrahedron Lett.* **1990**, *31*, 2805–2808.
8. Holmes, R. E.; Neel, D. A. *Tetrahedron Lett.* **1990**, *31*, 5567–5570.
9. Kim, K. S.; Ryan, P. *Heterocycles* **1990**, *31*, 79–86.
10. Ternansky, R. J.; Draheim, S. E. *Tetrahedron* **1992**, *48*, 777–796.
11. Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789–12854, and references cited therein.
12. Svete, J.; Prešeren, A.; Stanovnik, B.; Golič, L.; Golič Grdadolnik, S. *J. Heterocycl. Chem.* **1997**, *34*, 1323–1328.
13. Prešeren, A.; Svete, J.; Stanovnik, B. *J. Heterocycl. Chem.* **1999**, *36*, 799–801.
14. Svete, J.; Stanovnik, B. *Heterocycles* **1999**, *51*, 2073–2078.
15. Zupančič, S.; Svete, J.; Stanovnik, B. *J. Heterocycl. Chem.* **1999**, *36*, 607–610.
16. Stanovnik, B.; Svete, J. *Targets Heterocycl. Syst.* **2000**, *4*, 105–137.
17. Turk, C.; Svete, J.; Stanovnik, B.; Golič, L.; Golobič, A.; Selič, L. *Org. Lett.* **2000**, *2*, 423–424.
18. Turk, C.; Svete, J.; Stanovnik, B.; Golič, L.; Golič Grdadolnik, S.; Golobič, A.; Selič, L. *Helv. Chim. Acta* **2001**, *84*, 146–156.
19. Turk, C.; Golič, L.; Selič, L.; Svete, J.; Stanovnik, B. *ARKIVOC* **2001**, Part v, 87–97.
20. Svete, J. *J. Heterocycl. Chem.* **2002**, *39*, 437–454.
21. Pezdirc, L.; Jovanovski, V.; Bevk, D.; Jakše, R.; Pirc, S.; Meden, A.; Stanovnik, B.; Svete, J. *Tetrahedron* **2005**, *61*, 3977–3990.
22. Svete, J. *ARKIVOC* **2006**, Part vii, 35–56.
23. Pezdirc, L.; Cerkovnik, J.; Pirc, S.; Stanovnik, B.; Svete, J. *Tetrahedron* **2007**, *63*, 991–999.
24. *General Procedure*: All five reactions were carried out in a parallel synthesiser (Radley's Carousel 6 Reaction Station). Acetic acid (5 × 0.012 ml, 5 × 2 mmol) was added to the stirred mixtures of azomethine imines **4a–e** (5 × 2 mmol), potassium cyanide (5 × 195 mg, 5 × 3 mmol), and methanol (5 × 8 ml) and the mixtures were stirred at rt for 3 h. The precipitates were collected by filtration, washed with ether, and dried in vacuo to give compounds **6a–d** and **5e**.
25. *N-[(1R*,2R*)-3-Amino-2-benzamido-3-oxo-1-phenylpropyl]-benzimidoyl cyanide* (**6a**): Prepared from **1a** (738 mg,

2 mmol). Yield: 671 mg (85%) of a white solid; mp 253–255 °C. EI-MS: $m/z = 397$ (MH^+). ^{1}H NMR (DMSO-d_6): 5.24 (1H, t, $J = 9.5$ Hz, 2′-H); 5.49 (1H, d, $J = 9.5$ Hz, 1′-H); 7.14 (1H, s, $CONH_2$–H_a); 7.23 (1H, m, 1H of Ar); 7.32 (2H, m, 2H of Ar); 7.40 (2H, m, 2H of Ar); 7.49 (1H, m, 1H of Ar); 7.60 (6H, m, 5H of Ar, $CONH_2$–H_b); 7.72 (2H, m, 2H of Ar); 8.00 (2H, m, 2H of Ar); 8.83 (1H, d, $J = 9.5$ Hz, NH). ^{13}C NMR (DMSO-d_6): δ 57.7, 72.0, 109.6, 127.2, 127.4, 127.8, 127.9, 128.0, 128.2, 129.1, 131.2, 132.7, 132.8, 133.7, 139.0, 140.7, 165.8, 171.2. ν_{max} (KBr) 3360 (NH); 2222 (C≡N); 1699, 1653 (C=O); 1603, 1536 cm^{-1}. EI-HRMS: $m/z = 397.1665$ (MH^+); $C_{24}H_{21}N_4O_2$ requires: $m/z = 397.1655$ (MH^+).

26. *N-[(1R*,2R*)-3-Amino-2-benzamido-3-oxo-1-(4-methoxyphenyl)propyl]benzimidoyl cyanide* (**6b**): Prepared from **1b** (800 mg, 2 mmol). Yield: 300 mg (35%) of a white solid; mp 209–210 °C (from EtOH–DMF). EI-MS: $m/z = 427$ (MH^+). ^{1}H NMR (DMSO-d_6): 3.85 (3H, s, OMe); 5.20 (1H, t, $J = 9.4$ Hz, 2′–H); 5.44 (1H, d, $J = 9.4$ Hz, 1′-H); 7.11 (1H, s, $CONH_2$–H_a); 7.12 (2H, m, 2H of Ar); 7.22 (1H, m, 1H of Ar); 7.31 (2H, m, 2H of Ar); 7.40 (2H, m, 2H of Ar); 7.48 (1H, m, 1H of Ar); 7.59 (2H, m, 2H of Ar); 7.61 (1H, s, $CONH_2$–H_b); 7.72 (2H, m, 2H of Ar); 7.94 (2H, m, 2H of Ar); 8.81 (1H, d, $J = 9.4$ Hz, NH). ^{13}C NMR (DMSO-d_6): δ 55.5, 57.8, 71.8, 109.8, 114.6, 125.7, 127.2, 127.7, 127.9, 128.0, 128.2, 129.3, 131.2, 133.8, 139.4, 139.9, 162.8, 165.7, 171.3. (Found: C, 69.20; H, 5.19; N, 12.74. $C_{25}H_{22}N_4O_3 \cdot 1/3H_2O$ requires: C, 69.43; H, 5.28; N, 12.96.); ν_{max} (KBr) 3381 (NH); 2220 (C≡N); 1682, 1655 (C=O); 1599, 1574 cm^{-1}. EI-HRMS: $m/z = 427.1770$ (MH^+); $C_{25}H_{23}N_4O_3$ requires: $m/z = 427.1775$ (MH^+).

27. *N-[(1R*,2R*)-3-Amino-2-benzamido-3-oxo-1-(3,4,5-trimethoxyphenyl)propyl]benzimidoyl cyanide* (**6c**): Prepared from **1c** (918 mg, 2 mmol). Yield: 621 mg (64%) of a white solid; mp 216–218 °C (from EtOH–DMF). ^{1}H NMR (DMSO-d_6): 3.75 and 3.86 (9H, 2s, 1:2, 3 × OMe); 5.25 (1H, t, $J = 9.4$ Hz, 2′-H); 5.43 (1H, d, $J = 9.4$ Hz, 1′-H); 7.14 (1H, s, $CONH_2$–H_a); 7.23 (1H, m, 1H of Ar); 7.32 (4H, m, 4H of Ar); 7.41 (2H, m, 2H of Ar); 7.49 (1H, m, 1H of Ar); 7.59 (3H, m, 2H of Ar, $CONH_2$–H_b); 7.74 (2H, m, 2H of Ar); 8.83 (1H, d, $J = 9.4$ Hz, NH). ^{13}C NMR (DMSO-d_6): δ 56.0, 57.8, 60.2, 71.7, 105.0, 109.6, 127.3, 127.8, 127.9, 128.0, 128.2, 128.3, 131.2, 133.7, 139.2, 139.9, 141.4, 153.1, 165.8, 171.3. (Found: C, 66.87; H, 5.53; N, 11.22. $C_{27}H_{26}N_4O_5$ requires: C, 66.65; H, 5.39; N, 11.52.); ν_{max} (KBr) 3449, 3324 (NH); 2216 (C≡N); 1682, 1651 (C=O); 1606, 1581 cm^{-1}.

28. *N-[(1R*, 2R*)-3-Amino-2-benzamido-3-oxo-1-(2,6-dichlorophenyl)-propyl]benzimidoyl cyanide* (**6d**): Prepared from **1d** (876 mg, 2 mmol). Yield: 261 mg (28%) of a white solid; mp 215–217 °C (from EtOH–DMF). EI-MS: $m/z = 465$ (M^+). ^{1}H NMR (DMSO-d_6): 5.25 (1H, t, $J = 9.5$ Hz, 2′-H); 5.64 (1H, d, $J = 9.5$ Hz, 1′-H); 7.17 (1H, s, $CONH_2$–H_a); 7.25 (1H, m, 1H of Ar); 7.34 (2H, m, 2H of Ar); 7.41 (2H, m, 2H of Ar); 7.46 (1H, m, 1H of Ar); 7.53 (2H, m, 2H of Ar); 7.57 (1H, s, $CONH_2$–H_b); 7.63 (3H, m, 3H of Ar); 7.71 (2H, m, 2H of Ar); 8.83 (1H, d, $J = 9.5$ Hz, NH). ^{13}C NMR (DMSO-d_6): δ 55.9, 72.9, 109.4, 116.6, 127.2, 127.8, 127.9, 128.0, 128.1, 128.2, 128.9, 131.1, 133.0, 133.6, 136.9, 137.8, 165.5, 170.7. (Found: C, 61.94; H, 3.78; N, 11.96. $C_{24}H_{18}N_4O_2Cl_2$ requires: C, 61.95; H, 3.90; N, 12.04.); ν_{max} (KBr) 3359 (NH); 2238 (C≡N); 1692, 1654 (C=O); 1579, 1531 cm^{-1}.

29. *(1′S*,4R*,5R*)-4-Benzamido-1-[cyano(mesityl)methyl]-5-phenylpyrazolidin-3-one* (**5e**): Prepared from **1e** (876 mg, 2 mmol). Yield: 662 mg (76%) of a white solid; mp 377–378 °C. EI-MS: $m/z = 439$ (MH^+). ^{1}H NMR (DMSO-d_6): 2.12 and 2.31 (9H, 2s, 1:2, 3 × Me); 3.95 (1H, d, $J = 3.5$ Hz, 5-H); 4.23 (1H, dd, $J = 3.5$, 6.8 Hz, 4-H); 5.74 (1H, s, 1′-*H*); 6.77 (2H, s, 2H of Ar); 7.31 (3H, m, 3H of Ar); 7.55 (5H, m, 5H of Ar); 7.98 (2H, m, 2H of Ar); 9.59 (1H, d, $J = 6.8$ Hz, NH); 10.71 (1H, br s, 2-*H*). ^{13}C NMR (DMSO-d_6): δ 19.9, 20.2, 57.4, 59.3, 66.1, 117.3, 125.0, 126.0, 127.3, 127.4, 127.5, 128.3, 128.4, 129.9, 132.9, 137.7, 138.7, 139.2, 154.9, 161.7, 166.5. ν_{max} (KBr) 3309 (NH); 2243 (C≡N); 1721, 1641 (C=O); 1551 cm^{-1}. EI-HRMS: $m/z = 439.2134$ (MH^+); $C_{27}H_{27}N_4O_2$ requires: $m/z = 439.2140$ (MH^+).

30. Crystallographic data (excluding structure factors) for the structure of **6c** in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 644415. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 0 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.

31. Hesse, M.; Meier, H.; Zeeh, B. In *Spektroskopische Methoden in der Organische Chemie; 5. überarbeitete Auflage*; Georg Thieme: Stuttgart, 1995; p 134.

32. Zličar, M.; Huč, B.; Stanovnik, B.; Tišler, M. *Synlett* **1990**, 707–708.

33. Stanovnik, B. *Tetrahedron* **1991**, *47*, 2925–2945.