

UNPRECEDENTED REARRANGEMENT REACTION OF NITRILE OXIDES AND A STERICALLY CONGESTED 4-YLIDENE-5-ISOXAZOLONE

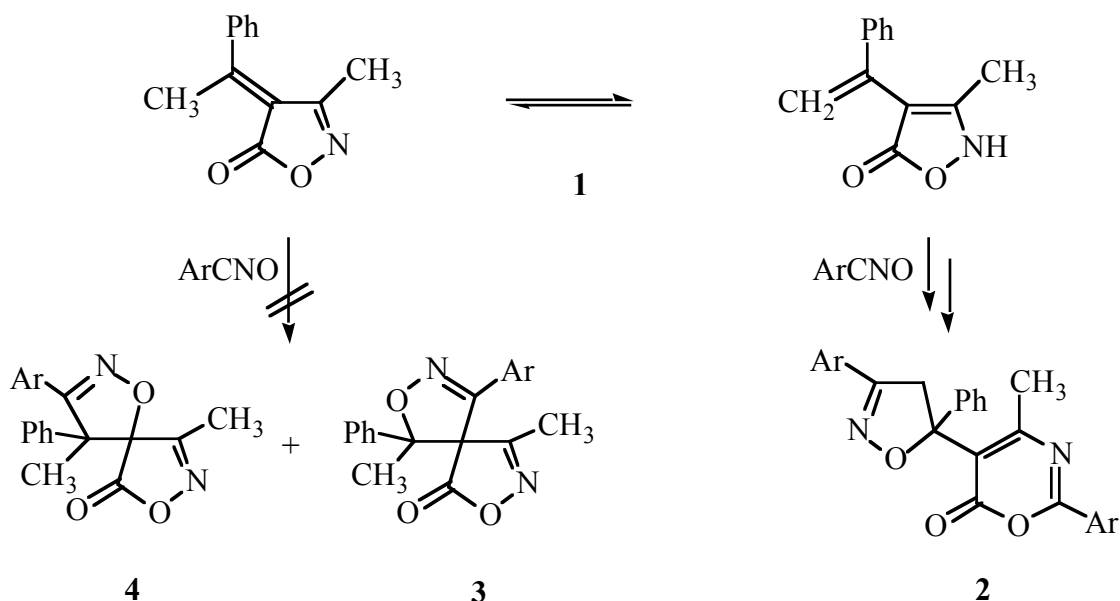
Francesco Foti,<sup>\*,a</sup> Giovanni Grassi,<sup>a</sup> Francesco Risitano,<sup>a</sup> Giuseppe Bruno,<sup>b</sup> and Francesco Nicolò<sup>b</sup>

<sup>a</sup>Dipartimento di Chimica Organica e Biologica, Università, Vill. S. Agata, I-98166 Messina, Italy. E-mail: ffoti@isengard.unime.it

<sup>b</sup>Dipartimento di Chimica Inorganica, Analitica e Struttura Molecolare, Università, Vill. S. Agata, I-98166 Messina, Italy

**Abstract** - The reaction between nitrile oxides and 4-diphenylmethylene-3-phenylisoxazol-5-one (**5**) proceeds in an unprecedented fashion to yield 4-diphenylmethylene-2,3,3-trisubstituted derivatives (**10**). Their structure was determined by an X-Ray diffraction study.

Functionally substituted isoxazol-5-ones have been successfully used to carry out a variety of synthetically useful transformations when treated with 1,3-dipoles. In particular, using nitrile oxides, it has been found that: (i) 4-arylmethylene isoxazol-5-ones are converted into spirocycloadducts by regioselective addition to the exocyclic double C-C bond;<sup>1</sup> and (ii) 4-arylmethylisoxazol-5-ones, capable of prototropic tautomerism, undergo ring enlargement to 1,3-oxazin-6-one.<sup>2</sup> The latter result can only be achieved when the isoxazol-5-one substrate reacts in its N-H form. Indeed, the reaction of 3-methyl-4-(1-phenylethylidene)-4*H*-isoxazol-5-one (**1**) with nitrile oxide gave 5-isoxazoliny-1,3-oxazin-6-one (**2**) instead of the expected spiro-compounds (**3**) and/or (**4**) (Scheme 1).<sup>3</sup> This mode of reaction was attributed to steric hindrance around the arylidene C-C double bond.<sup>4</sup>



Scheme 1

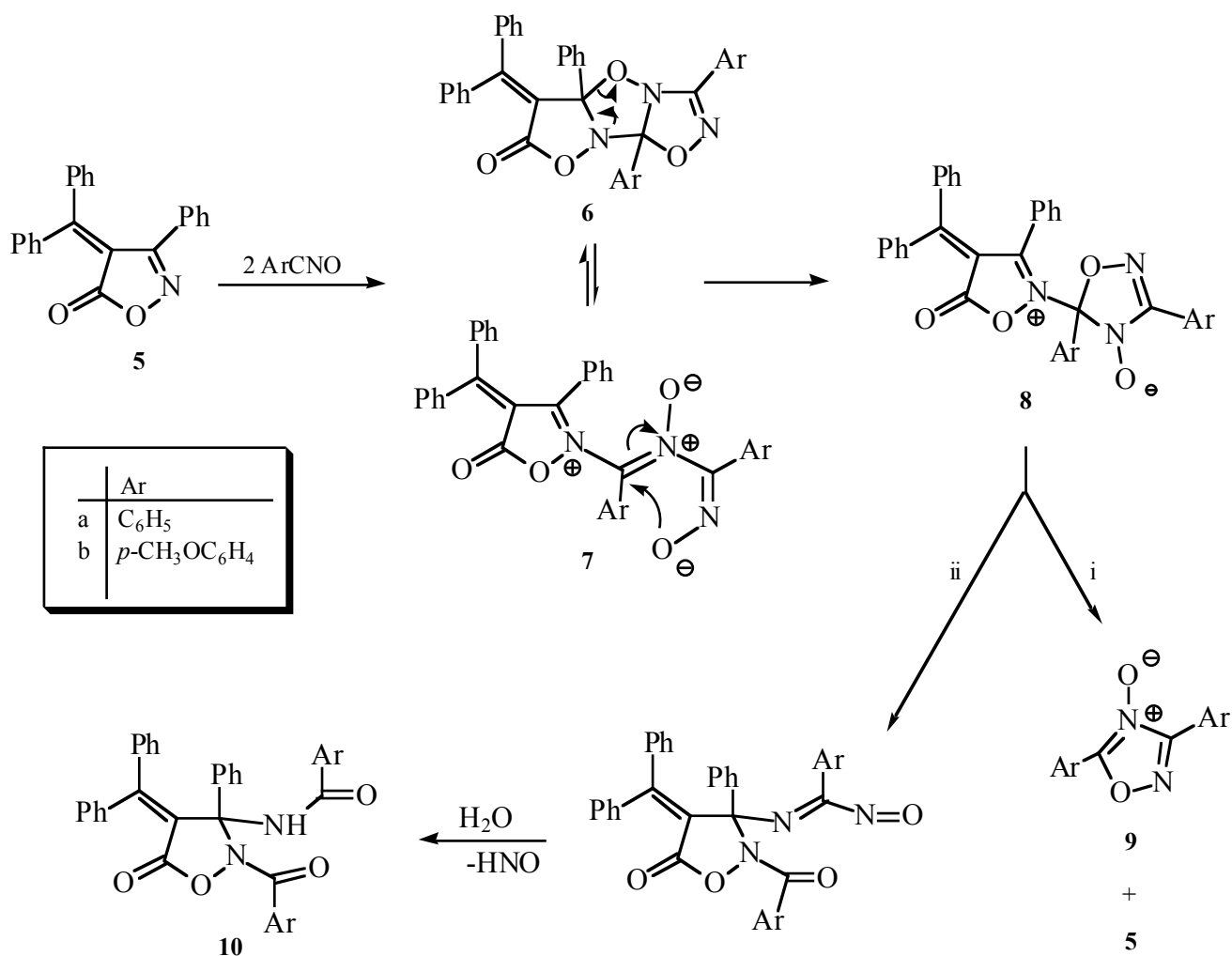
These results prompted us to extend our study of nitrile oxide to 4-diphenylmethylene-3-phenylisoxazol-5-one (**5**),<sup>5</sup> a substrate incapable of prototropic tautomerism containing bulky substituents on the exocyclic C-C double bond. Thus, the reaction of **5** with benzonitrile oxide afforded 3,4-diphenylfuroxane,<sup>6</sup> 3,5-diphenyl-1,2,4-oxadiazole 4-oxide (**9a**),<sup>7</sup> the starting isoxazolone (**5**), and a white crystalline derivative (**10a**) in poor yield. This last compound had a mp of 218°C, a molecular weight of 550 and the formula C<sub>36</sub>H<sub>26</sub>O<sub>4</sub>N<sub>2</sub>. The IR spectrum showed a sharp N-H band at 3410 cm<sup>-1</sup>, and three carbonyl peaks at 1795, 1680 and 1650cm<sup>-1</sup>; the first was related to an azalactone carbonyl, and the others to amide carbonyls. The <sup>1</sup>H-NMR spectrum showed only aromatic protons between 6.5 and 8.0 ppm.

Although the above mentioned results gave us an idea of the structure of the compound, we decided to carry out an experiment to determine the exact benzonitrile oxide equivalents required for transformation. Thus, the reaction was repeated using 4-methoxybenzonitrile oxide and a new product (**10b**), similar to the previous one with a mp of 200°C, a molecular weight of 610 and the formula C<sub>38</sub>H<sub>30</sub> N<sub>2</sub>O<sub>6</sub>, was isolated alone with 3,4-bis(4-methoxyphenyl)furoxane,<sup>6</sup> 3,5-bis(4-methoxyphenyl)-1,2,4-oxadiazole 4-oxide (**9b**),<sup>8</sup> and the starting isoxazolone (**5**). As well as an aromatic region between 6.5 and 8.1 ppm, the <sup>1</sup>H-NMR spectrum of **10b**, showed two more singlets at 3.99 and 4.03 ppm. Consequently the substrate/nitrile oxide ratio was deduced to be 1/2.

The structure of the compounds (**10**) was fully determined by an X-Ray crystallographic analysis carried out on **10a** (Figure 1).<sup>9</sup> The compound is made up of a central 5-membered isoxazolidin-5-one ring containing an asymmetric carbon atom (C3) which binds a phenyl and a benzamide group. The two adjacent atoms, N1 and C2, are linked to a benzoyl and a diphenylmethylene group, respectively. Since the compound crystallizes in the C2/c centrosymmetric space group, the crystallographic asymmetric unit contains both *R* and *S* enantiomers, giving a racemic mixture in the solid state.

The geometric values of the 5-membered ring are consistent with values for a similar structure previously described.<sup>10</sup> The carbonyl bond angles show the usual asymmetry (O(1)-C(1)-O(2) = 118.5(3)° vs. O(2)-C(1)-C(2) = 132.5(4)°), which we have already pointed out to be caused by steric and electronic factors.<sup>11</sup> Both the asymmetric carbon groups are almost coplanar and orthogonal to the isoxazolidinone plane. The benzamide fragment is flatted by extended  $\pi$ -delocalization and makes a dihedral angle of 87.7(3)° with respect to the 5-membered ring. The geometry of the C(4) and C(17) sp<sup>2</sup> carbon atoms is almost equal (N-C, C-Ph and C=O are 1.352(4), 1.492(5) and 1.223(4)Å vs. 1.358(4), 1.491(5) and 1.216(4)Å, respectively). The N1 nitrogen is not pyramidalized and, as evidenced by the torsion angle O(1)-N(1)-C(17)-O(4) of -178.9(3)°, the C(1)-O(1)-N(1) fragment is coplanar with the flat -COPh group producing extended electronic delocalization over the O(2)-C(1)-O(1)-N(1)-C(17)-O(4) fragment. Delocalization explains the fact that the O(1)-N(1) bond distance of 1.421(3)Å is significantly shorter than the distance of 1.491(2)Å reported in literature.<sup>12</sup>

Consistent with previous results<sup>13</sup> as illustrated in Scheme 2, this reaction most likely involves initial formation of the bis-cycloadduct (**6**), and/or of the open-chain bis-adduct (**7**), and proceeds through the intermediacy of the zwitterion (**8**). This can break down (path i) into 1,2,4-oxadiazole 4-oxide (**9**) and starting material (**5**) or rearrange (path ii)<sup>14</sup> to yield (**10**).



Scheme 2

## EXPERIMENTAL

Melting points were determined with Reichert-Kofler hot stage apparatus and are uncorrected. IR spectra were obtained using a Nicolet FT-IR Impact 400D spectrophotometer, MS spectra using a Finnigan Mat 90 spectrometer and microanalyses for C, H, and N using a Carlo Erba 1102. <sup>1</sup>H NMR were recorded using a Bruker ARX 300 spectrometer, in the solvent indicated. Chemical shifts (δ) refer to TMS, which was used as an internal reference. Column chromatography was performed on Merck silica gel 70-270 mesh. All solvents and reagents were obtained from commercial sources and purified before use if necessary. Benzo and *p*-anisohydroximoyl chlorides were prepared according to literature.<sup>15</sup>

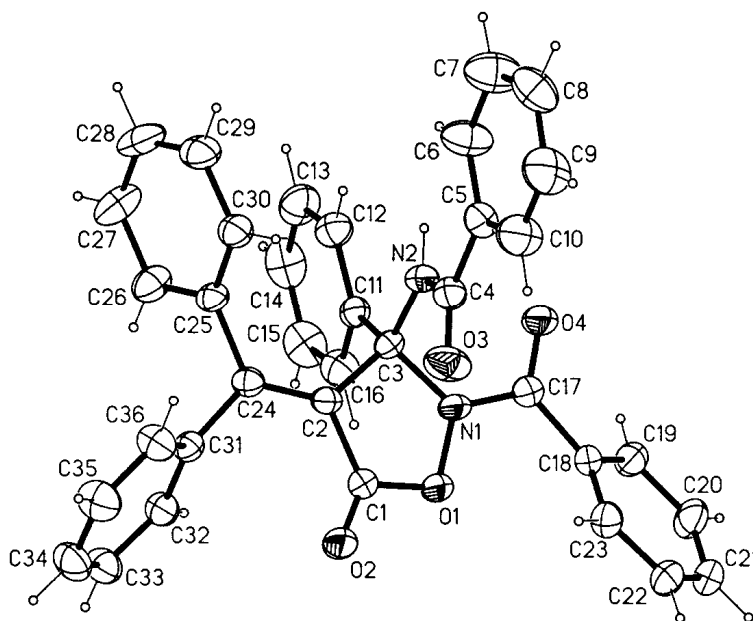
### 4-Diphenylmethylene-2,3,3-trisubstituted derivatives (10); General Procedure:

A solution of triethylamine (1.01 g, 10 mmol) in 1,4-dioxane (20 mL) was added dropwise to a solution of 4-diphenylmethylene-3-phenylisoxazol-5-one (**5**) (6.0 g, 30 mmol) and the appropriate hydroximoyl chloride (**a**: 1.6 g, 10 mmol; **b**: 1.9 g, 10 mmol) in 1,4-dioxane (150 mL). The mixture was refluxed for 3h. Then the precipitate was filtered and the resulting solution was concentrated under the reduced pressure.

The residue was chromatographed on silica gel (chloroform as eluent) to give **10**:

**10a**: colorless solid; mp 218°C (methanol); 880 mg (16%); EIMS  $m/z$  550 ( $M^+$ ); IR(nujol): 3410, 1795, 1680, 1650  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$  6.5-8.0 (m, 25H). Anal. Calcd for  $\text{C}_{36}\text{H}_{26}\text{N}_2\text{O}_4$ : C, 78.53, H, 4.76, N, 5.51. Found: C, 78.40, H, 4.65, N, 5.42.

**10b**: colorless solid; mp 200°C (methanol); 920 mg (15%); EIMS  $m/z$  610 ( $M^+$ ); IR(nujol): 3405, 1790, 1670, 1645  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$  3.99 (s, 3H), 4.03 (s, 3H), 6.5-8.1 (m, 23H). Anal. Calcd for  $\text{C}_{38}\text{H}_{30}\text{N}_2\text{O}_6$ : C, 74.74, H, 4.95, N, 4.59. Found: C, 74.91, H, 4.99, N, 4.68.



**Figure 1.** View of the compound (**10a**) showing the atomic numbering scheme. Displacement ellipsoids are drawn at 30% of probability level while H size is arbitrary. Selected bonds ( $\text{\AA}$ ) and angles ( $^\circ$ ): N1-C17 = 1.352(4); N1-O1 = 1.421(3); N1-C3 = 1.488(4); O1-C1 = 1.379(4); C1-O2 = 1.189(4); C1-C2 = 1.470(5); C2-C24 = 1.338(4); C2-C3 = 1.528(5); C3-N2 = 1.439(4); C3-C11 = 1.521(5); N2-C4 = 1.358(4); C4-O3 = 1.223(4); C17-N1-O1 = 120.4(3); C17-N1-C3 = 125.8(3); O1-N1-C3 = 113.6(3); C1-O1-N1 = 108.1(2); O2-C1-O1 = 118.5(3); O2-C1-C2 = 132.5(4); O1-C1-C2 = 109.1(3); N2-C3-N1 = 109.7(3); N2-C3-C11 = 112.0(3); N2-C3-C2 = 114.0(3); C4-N2-C3 = 121.2(3); O4-C17-N1 = 117.5(3); N1-C17-C18 = 119.7(3); C17-N1-O1-C1 = 173.3(3); N1-O1-C1-O2 = -175.0(3); O2-C1-C2-C24 = -11.8(7); O1-C1-C2-C24 = 167.3(3); O2-C1-C2-C3 = 173.3(4); O1-C1-C2-C3 = -7.7(4); O1-N1-C17-O4 = -178.9(3); C3-N2-C4-O3 = -0.1(5); C1-C2-C24-C31 = -5.4(6).

**Crystal Structure Determination of 10a:** – Crystal data.  $\text{C}_{36}\text{H}_{26}\text{N}_2\text{O}_4$ ,  $M_r=550.61$ , monoclinic,  $\text{C}2/c$ ,  $a=27.319(5)$ ,  $b=11.177(2)$ ,  $c=18.622(4)$   $\text{\AA}$ ,  $\beta=99.24(3)^\circ$ ,  $V=5612(2)$   $\text{\AA}^3$ ,  $Z=8$ ,  $D_c=1.303$   $\text{g cm}^{-3}$ ,  $\lambda(\text{MoK}\alpha) = 0.71073$   $\text{\AA}$ ,  $\mu=0.085$   $\text{mm}^{-1}$ ,  $F(000)=2304$ ,  $T=296$  K,  $R_1=0.0535/0.1085$  for 2225/3686 obs/all independent reflections.

Crystals suitable for X-Ray analysis were obtained by recrystallization from methanol solutions. A crystal of dimensions 0.20 x 0.20 x 0.30 mm was used for intensity-data collection at room temperature using a Siemens P4 four-circle diffractometer and graphite-monochromated MoK $\alpha$  radiation ( $\lambda = 0.71073$   $\text{\AA}$ ). 3775 reflections were measured by the  $\omega/2\theta$  scan technique up to  $2\theta=46^\circ$  ( $0 < h < 29$ ,  $0 < k < 12$ ,  $-20 < l$

<19). Diffraction data were processed using the learnt-profile procedure<sup>15</sup> and then corrected for Lorentz-polarization effects. Absorption correction was applied by fitting a pseudo-ellipsoid to the azimuthal scan data of 15 suitable reflections with high  $\chi$  angles.<sup>16</sup>

The structure was solved by standard direct methods and subsequently completed by a combination of least squares technique and Fourier Syntheses. All non-hydrogen atoms were refined anisotropically.

Hydrogens were located on idealized positions and allowed to ride on their parent carbon atoms. The structure model was refined using the full-matrix least squares technique for all the independent 3686  $F^2$  data, minimizing the function  $\sum w(F_o^2 - F_c^2)^2$ . The refinement converged up to R1 and R2 values of 0.1085 and 0.1247 for all independent data set, and 0.0535 and 0.1006 for the 2225 reflections with  $I \geq 2\sigma(I)$ , respectively, while the goodness-of-fit is 1.015. The last difference map showed the largest electron density residuals (max and min range =  $\pm 0.20 \text{ e}\text{\AA}^{-3}$ ). Neutral-atom scattering factors and anomalous dispersion corrections were taken into account.<sup>17</sup>

Data reduction and structure solutions and drawings were performed with the SHELXTL-PLUS package,<sup>18</sup> while structure refinement and final geometrical calculations were carried out with SHELXL-97<sup>19</sup> and PARST programs,<sup>20</sup> respectively.

## REFERENCES AND NOTES

1. G. Lo Vecchio, G. Cum, and G. Stagno D'Alcontres, *Gazz. Chim. Ital.*, 1965, **95**, 127; b) G. Lo Vecchio, G. Cum, and G. Stagno D'Alcontres, *Gazz. Chim. Ital.*, 1965, **95**, 206; c) G. Lo Vecchio, G. Grassi, F. Risitano, and F. Foti, *Tetrahedron Lett.*, 1973, 3777; d) G. Lo Vecchio, F. Risitano, G. Grassi, F. Foti, and F. Caruso, *Atti Acc. Peloritana Pericolanti*, 1974, **54**, 297.
2. G. Lo Vecchio, F. Foti, G. Grassi, and F. Risitano, *Tetrahedron Lett.*, 1977, 2119.
3. F. Risitano, G. Grassi, F. Foti, F. Caruso, and G. Lo Vecchio, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1522.
4. R. Huisgen, *Angew. Chem.*, 1963, **75**, 604.
5. A. H. Harhash, M. H. Elnagdi, N. S. Tunsu Hussein, and S. M. Fahmy, *Indian J. Chem.*, 1973, **11**, 1.
6. The reaction competed obviously with the unavoidable dimerisation of the nitrile oxide to the corresponding furoxane.
7. G. Speroni and M. Bartoli "Sopra gli ossidi di benzonitrile", nota VIII, Stabilimento Tipografico Marzocco, Firenze, 1952.
8. C. R. Kinney, E. W. Smith, B. L. Woolley, and A. R. Willey, *J. Am. Chem. Soc.*, 1933, **55**, 3418.
9. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 155618. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
10. F. Risitano, G. Grassi, G. Bruno, and F. Nicolò, *Liebigs Ann. Chem.*, 1997, 441.
11. G. Bruno, F. Nicolò, A. Rotondo, F. Foti, F. Risitano, G. Grassi, and C. Bilardo, *Acta Crystallogr., Sect. C*, in press.

12. Panfil, Z. Urbanczyk-Lipkowska, and M. Chmielewski, *Carbohydr. Res.*, 1998, **306**, 505.
13. G. Grassi and F. Risitano, 'Targets in Heterocyclic Systems', Vol.1, ed. by O. A. Attanasi and D. Spinelli, SCI, 1997, pp.141-160 and references cited therein.
14. The gaseous product underwent areal oxidation and  $N_2O_4$  was detected in the reflux condenser.
15. Ch. Grundmann and P. Grunanger, 'The Nitrile Oxides', Springer-Verlag Berlin, 1971, p. 48 and references cited therein.
16. R. Diamond, *Acta Crystallogr., Sect. A*, 1969, **27**, 43
17. G. Kopfmann and R. Huber, *Acta Crystallogr., Sect. A*, 1968, **24**, 348
18. *International Tables for X-Ray Crystallography*, Volume C, ed. by A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992.
19. *SHELXTL-PLUS*, version 4.2, Siemens Analytical X-ray Instruments Inc., Madison Wisconsin, 1991.
20. G. M. Sheldrick, *Acta Crystallogr., Sect. A*, 1990, **46**, 467; b) G. M. Sheldrick, Z. Dauter, K. S. Wilson, H. Hope, and L. C. Sieker, *Acta Crystallogr., Sect. D*, 1993, **49**, 18
21. M. Nardelli, *J. Appl. Cryst.*, 1995, **28**, 659. (Version locally modified).