SHORT PAPER

J. Chem. Research (S), 2000, 426–428

Preparation of 2,5-iminoazepines via the imine–ene reaction of 3-allylamino-2-(substituted)acrolein imines†

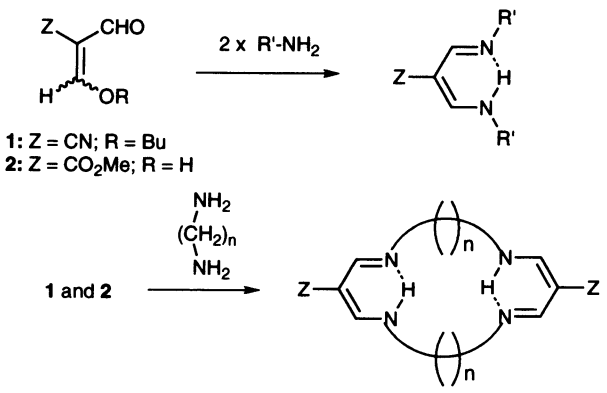
Shinji Takamura,[a] Hisashi Yamada,[a] Takanori Michinaka,[a] Hidetoshi Yamamoto,[a] Akikazu Kakehi,[b] and Michihiko Noguchi[a]*

[a]*Department of Applied Chemistry, Faculty of Engineering, Yamaguchi University, Tokiwadai, Ube 755-8611, Japan*

[b]*Department of Chemistry and Material Engineering, Faculty of Engineering, Shinshu University, Wakasato, Nagano 380-8553, Japan*

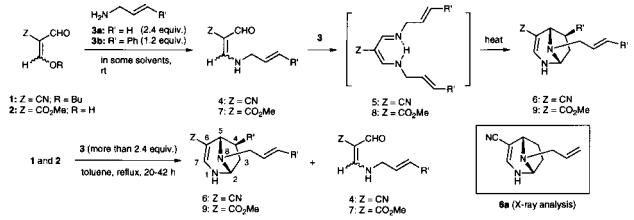
Malonaldehyde derivatives **1** and **2** with an excess of allylamine (**3a**) in refluxing toluene gave 2,5-iminoazepines **6a** and **9a** in moderate yields via the thermal imine–ene reaction of the initially formed vinamidines **5a** and **8a**.

We have studied the reaction of 2-(substituted)malonaldehyde derivatives **1** and **2** with primary amines and will report elsewhere the formation of vinamidines[1] and their physical properties.[2] More recently, we have also reported that the reaction of malonaldehyde derivatives **1** and **2** with 1,ω-diaminoalkanes gave macrocycles containing the vinamidine moiety through the (2:2) cyclocondensation.[3] Therefore, we investigated the reaction of malonaldehyde derivatives **1** and **2** with allylamine (**3a**), expecting formation of the vinamidine bearing allyl groups on both termini (Scheme 1).



Scheme 1

The reaction of 2-cyano-3-butoxyacrolein **1**, obtained by acid-treatment of 1,3,3-tributoxy-2-cyanopropene,**4** with allylamine (**3a**: 2.4 equiv.) in THF at room temp. gave 3-allylamino-2-cyanoacrolein (**4a**) in almost quantitative yield. Further reaction of acrolein **4a** with an excess of allylamine (**3a**), aiming for vinamidine **5a**, was examined; in some solvents at room temperature with or without dehydrating reagents only the unreacted **4a** was recovered. Monitoring of the reaction progress by TLC suggested the formation of the desired vinamidine **5a** from **4a** and **3a**, but usual work-up with column chromatography on silica gel gave also the unreacted **4a**. These findings meant that a facile hydrolysis of vinamidine **5a** to acrolein **4a** and allylamine (**3a**) took place under the reaction conditions or during work-up procedures. On the other hand, the reaction of **4a** with **3a** (2.4 equiv.) in toluene under reflux successfully gave product **6a** in 42% yield together with the recovered **4a** (36%). One step reaction of **1** with a large excess of **3a** in toluene under reflux gave an almost same result (**6a**: 46%). The structure of **6a** was deduced to be 8-allyl-6-cyano-2,3,4,5-tetrahydro-2,5-imino-1*H*-azepine from its analytical and spectroscopic data. Although its molecular formula [$C_{10}H_{13}N_3$; *m/z* = 175 (M^+)] corresponded to those of vinamidine **5a**, ^{1}H and ^{13}C NMR spectra of **6a** showed that it bears only one allyl moiety. Fortunately, the structure of a crystalline **6a** was confirmed unambiguously by X-ray single-crystal structure analysis.[5]



Scheme 2

Table 1 One step preparation of 2,5-iminoazepines **6** and **9** by the reaction of acrolein derivatives **1** and **2** with allylamines **3**

Run	Acrolein	Amine/ equiv.	Time/h[a]	Products/Yield (%)[b]	
1	**1**	**3a**/ > 8	20	**6a**/46	**4a**/38
2	**1**	**3b**/2.4	42	**6b**/42	**4b**/30
3	**2**	**3a**/ > 8	20	**9a**/36	**7a**/22
4	**2**	**3b**/2.4	20	**9b**/40	**7b**/34

[a]Performed in toluene under reflux. [b]Based on isolated products.

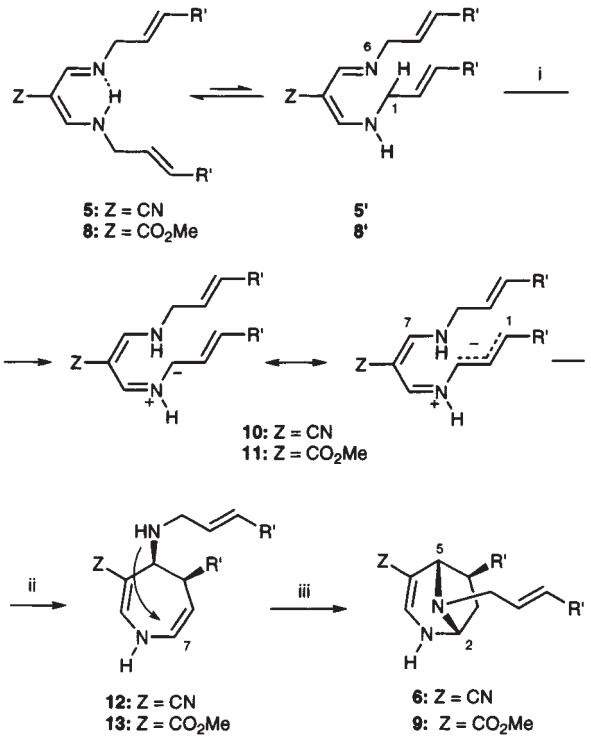
A similar reaction of aldehyde **1** and cinnamylamine (**3b**) with stepwise or one step procedures gave 2,5-iminoazepine **6b** in moderate yield. Reaction of 2-(methoxycarbonyl)-malonaldehyde **2**[6] with a large excess of **3a** in toluene under reflux gave 2,5-iminoazepine **9a** in 36% yield. A similar reaction of acrolein **7b** with amine **3b** (2.4 equiv.) also gave 2,5-iminoazepine **9b** in 40% yield. One step procedures of the reaction of acrolein **2** with allyl amines **3a** and **3b** gave slightly better results (Scheme 2 and Table 1).

The formation of iminoazepines **6** and **9** was explained by the formal imine–ene reaction of vinamidines **5** and **8** as discussed previously on the related 3-[*N*-(substituted)allylamino]-2-(substituted)acrolein derivatives:[7] thermal reaction of symmetric vinamidines **5** and **8** gave the less stable configurational isomers **5′** and **8′**. A 1,6-shift of the allylic hydrogen to the imine nitrogen in **5′** and **8′** gave conjugated azomethine ylide intermediates **10** and **11**, which underwent 1,7-electrocyclization gave azepine derivatives **12** and **13**. Nucleophilic attack of the amino nitrogen to the 7-position in **12** and **13**

* To receive any correspondence.

† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

afforded the final products **6** and **9** (Scheme 3). It should be emphasized that vinamidines **5** and **8** which had a secondary allylamino moieties underwent an thermal imine–ene reaction through the isomeric 3-allylamino-2-(substituted)acrolein imines **5′** and **8′** and that NH-azomethine ylides **10** and **11** as well as the corresponding N-substituted ones[7] were postulated as key intermediates in azepine ring formation.



Reactions: i, 1,6-H shift; ii, 1,7-electrocyclization; iii, nucleophilic attack of amino nitrogen onto the 7-position

Scheme 3

Experimental[8]

One-pot procedures for preparation of iminoazepine ***6a****;* a solution of 1,3,3-tributoxy- 2-cyanopropene (1.13 g, 4.0 mmol) and acetic acid (0.24 ml, 4.0 mmol) in THF (10ml) was stirred at room temp. for 12 h. To remove the excess acetic acid, potassium carbonate (0.76 g, 4.8 mmol) was added to the mixture and the mixture was stirred for additional 1 h. The mixture was extracted with ether and the solvent was evaporated at room temp to give 3-butoxy-2-cyanoacrolein (**1**; 0.27 g, 45%). A solution of acrolein derivative **1** (0.30 g, 2.0 mmol) and allylamine (**3a**; 0.15 ml, 2.0 mmol) in toluene (5 ml) was heated under reflux for totally 20 h and additional allylamine (**3a**; 0.15 ml × 3, 6.0 mmol) was added to the reaction mixture at every 3 hours. Usual work-up gave iminoazepine **6a** (46%) and acrolein derivative **4a** (38%).

3-Allylamino-2-cyanoacrolein (**4a**): pale yellow prisms from EtOH; m.p. 49–50°C; IR (KBr) ν_{max} = 3400, 2200, 1700, 1600 cm^{-1}. $C_7H_8N_2O$ (136.2): calcd. C, 61.75; H, 5.92; N, 20.58%; found C, 61.55; H, 5.87; N, 20.53%. This compound was a 5:1 mixture of two geometric isomers in $CDCl_3$. ^{1}H NMR ($CDCl_3$): major isomer: δ = 4.01 (2 H, overlapped (ov) >NC*H*$_2$CH=), 5.27–5.35 (2 H, ov, =CH$_2$), 5.81–5.97 (1 H, ov, –C*H*=CH$_2$), 7.44 (1 H, dd, *J* = 3.3 and 10.6 Hz, 3-H), 9.29 (1 H, d, *J* = 3.3 Hz, 1-H), 10.55 (1 H, br, NH). Assigned signals for minor isomer: δ = 7.88 (br, 3-H), 9.11 (br, 1-H); ^{13}C ($CDCl_3$): δ = 51.8 (>N*C*H$_2$CH=), 83.1 (2-C), 118.2 (CN), 119.2 (=CH$_2$), 131.5 (–*C*H=CH$_2$), 159.0 (3-C), 187.5 (1-C).

8-Allyl-6-cyano-2,3,4,5-tetrahydro-2,5-imino-1*H*-azepine (**6a**): colorless needles from hexane–benzene; m.p. 120–122°C; IR (KBr) ν_{max} = 3330, 2190, 1700, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 1.90–2.15 (2 H, ov, 3-H2), 2.15–2.30 (2 H, ov, 4-H$_2$), 3.00–3.15 (2 H, ov, >NC*H*$_2$CH=), 3.45 (1 H, br d, *J* = 4.0 Hz, 5-H), 4.20 (1 H, br t, *J* = 4.0 Hz, 2-H), 4.82 (1 H, br, NH), 5.13–5.27 (2 H, ov, =CH$_2$), 5.92 (1 H, m, –C*H*=CH$_2$), 6.90 (1 H, d, *J* = 5.6 Hz, 7-H); ^{13}C ($CDCl_3$): δ = 37.1, 37.3 (3- and 4-C), 49.4 (>NC*H*$_2$CH=), 57.7 (5-C), 68.5 (2-C), 79.2 (6-C), 117.8 (=CH$_2$), 121.5 (CN), 134.8 (–*C*H=CH$_2$), 141.7 (7-C); MS (EI): *m/z* = 175 (M$^+$, base peak). $C_{10}H_{13}N_3$ (175.2): calcd. C, 68.54; H, 7.48; N, 23.98%; found C, 68.68; H, 7.54; N, 23.81%.

Physical and spectral data for **4b**, **6b**, **7a**, **7b**, **9a** and **9b** as follows: *3-cinnamylamino-2-cyano-acrolein* (**4b**): colourless needles from EtOH; m.p. 141°C; IR (KBr) ν_{max} = 3160, 2200, 1620 cm^{-1}. $C_{13}H_{12}N_2O$ (212.3): calcd. C, 73.56; H, 5.70; N, 13.20%; found C, 73.55; H, 5.80; N, 13.23%. This compound was a (6:1) mixture of two geometric isomers in $CDCl_3$. ^{1}H NMR ($CDCl_3$): major isomer: δ = 4.12 (2 H, m, >NC*H*$_2$CH=), 6.15 (1 H, td, *J* = 6.0 and 15.8 Hz, –C*H*=CH-Ph), 6.60 (1 H, d, *J* = 15.8 Hz, –CH=C*H*-Ph), 7.30-7.37 (5 H, ov, Ph), 7.46 (1 H, d, *J* = 3.3 Hz, 3-H), 9.31 (1 H, d, *J* = 3.3 Hz, 1-H), 10.66 (1 H, br, NH). Assigned signals for minor isomer: δ = 6.63 (d, *J* = 15.6 Hz, –CH=C*H*–Ph), 9.14 (br, 1-H); ^{13}C ($CDCl_3$): δ = 51.7 (>N*C*H$_2$CH=), 83.6 (2-C), 119.3 (CN), 121.9, 126.6, 128.6, 128.7, 135.3 (Ph-C and –*C*H=CH–Ph), 135.2 (–CH=*C*H–Ph), 158.7 (3-C), 187.9 (1-C).

8-Cinnamyl-6-cyano-4-phenyl-2,3,4,5-tetrahydro-2,5-imino-1H-azepine (**6b**): colourless needles from EtOH; m.p. 38–39°C; IR (KBr) ν_{max} = 3280, 2190, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 2.16–2.28 (1 H, m, 3-H), 2.56 (1 H, dd, *J* = 9.2 and 13.5 Hz, 3-H), 3.28–3.31 (2 H, ov, >NC*H*$_2$CH=), 3.49 (1 H, s, 5-H), 3.63 (1 H, dd, *J* = 4.0 and 9.2 Hz, 4-H), 4.39 (1 H, dd, *J* = 4.3 and 4.6 Hz, 2-H), 4.96 (1 H, br, NH), 6.33 (1 H, td, *J* = 6.3 and 15.8 Hz, –C*H*=CH–Ph), 6.55 (1 H, d, *J* = 15.8 Hz, –CH=C*H*–Ph), 6.97 (1 H, d, *J* = 5.6 Hz, 7-H), 7.17–7.44 (10 H, ov, Ph); ^{13}C ($CDCl_3$): δ = 47.4 (3-C), 48.7 (>N*C*H$_2$CH=), 56.0 (4-C), 64.4 (5-C), 69.2 (2-C), 78.7 (6-C), 121.4 (CN), 126.2, 126.4, 126.5, 126.5, 126.8, 127.0, 128.4, 128.5, 136.8, 136.8, 145.6 (Ar-C), 127.0 (–*C*H=CH–Ph), 132.6 (–CH=*C*H–Ph), 141.7 (7-C). $C_{22}H_{21}N_3$ (273.4): calcd. C, 80.70; H, 6.47; N, 12.84%; found C, 80.55; H, 6.52; N, 12.98%.

3-Allylamino-2-(methoxycarbonyl)acrolein (**7a**): colourless prisms from EtOH; m.p. 37–38°C; IR (KBr) ν_{max} = 3400, 1720, 1600 cm^{-1}. $C_8H_{11}NO_3$ (169.2): calcd. C, 56.79; H, 6.55; N, 8.28%; found C, 56.64; H, 6.58; N, 8.34%. This compound was a (4:1) mixture of two geometric isomers in $CDCl_3$. ^{1}H NMR ($CDCl_3$): major isomer: δ = 3.76 (3 H, s, OMe), 3.97 (2 H, ov, >NC*H*$_2$CH=), 5.24–5.32 (2 H, ov, =CH$_2$), 5.88 (1 H, m, –C*H*=CH$_2$), 7.93 (1 H, dd, *J* = 3.6 and 14.2 Hz, 3-H), 9.82 (1 H, d, *J* = 3.6 Hz, 1-H), 10.79 (1 H, br, NH). Assigned signals for minor isomer: δ = 3.80 (s, OMe), 7.95 (d, *J* = 14.5 Hz, 3-H), 9.74 (s, 1-H). 13C ($CDCl_3$): major isomer: δ = 50.1 (OMe), 51.9 (>N*C*H$_2$CH=), 100.9 (2-C), 118.7 (=CH$_2$), 132.3 (–*C*H=CH$_2$), 158.9 (3-C), 167.7 (CO$_2$), 190.4 (1-C). Assigned signals for minor isomer: δ = 50.8 (OMe), 51.8 (>N*C*H$_2$CH=), 100.5 (2-C), 158.0 (3-C), 169.5 (CO$_2$), 187.4 (1-C).

8-Allyl-6-(methoxycarbonyl)-2,3,4,5-tetrahydro-2,5-imino-1*H*-azepine (**9a**): pale yellow oil; IR (NaCl) ν_{max} = 3400, 1720, 1600 cm^{-1}; 1H NMR ($CDCl_3$): δ = 1.94–2.02, 2.13–2.19 (each 2 H, each ov, 3-H$_2$ and 4-H$_2$), 3.02, 3.05 (each 1 H, each m, >NC*H*$_2$-CH=), 3.66 (3 H, s, OMe), 3.86 (1 H, br d, *J* = 5.3 Hz, 5-H), 4.18 (1 H, dd, *J* = 4.0 and 4.6 Hz, 2-H), 4.81 (1 H, br, NH), 5.09–5.20 (2 H, ov, =CH$_2$), 5.96 (1 H, m, –C*H*=CH$_2$), 7.34 (1 H, d, *J* = 5.6 Hz, 7-H); ^{13}C ($CDCl_3$): δ = 37.1 (4-C), 37.2 (3-C), 49.5 (>*C*H$_2$CH=), 50.5 (OMe), 56.1 (5-C), 68.6 (2-C), 100.3 (6-C), 117.3 (=CH$_2$), 135.5 (–*C*H=CH$_2$), 139.8 (7-C), 168.0 (CO$_2$). $C_{11}H_{16}N_2O_2$ (208.3): calcd. C, 56.79; H, 6.55; N, 8.28%; found C, 56.64; H, 6.58; N, 8.34%.

3-Cinnamylamino-2-cyanoacrolein (**7b**): colourless needles from hexane; m.p. 73–74 °C; IR (KBr) ν_{max} = 3300, 1720, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 3.77 (3 H, s, OMe), 4.11–4.16 (2 H, ov, >NC*H*$_2$CH=), 6.18 (1 H, td, *J* = 6.0 and 15.8 Hz, –C*H*=CH–Ph), 6.50 (1 H, d, *J* = 15.8 Hz, –CH=C*H*–Ph), 7.96 (1 H, dd, *J* = 3.3 and 13.9 Hz, 3-H), 9.84 (1 H, d, *J* = 3.3 Hz, 1-H), 10.85 (1 H, br, NH); ^{13}C ($CDCl_3$): δ = 51.1 (OMe), 51.8 (>N*C*H$_2$CH=), 101.0 (2-C), 123.0 (–*C*H=CH–Ph), 126.6, 128.4, 128.7, 135.6 (Ph-C), 124.2 (=*C*H-Ph), 158.7 (3-C), 167.7 (CO$_2$), 190.5 (1-C). $C_{14}H_{15}NO_3$ (245.3): calcd. C, 68.55; H, H,6.11; N, 5.71%; found C, 68.25; H, 6.21; N, 5.83%.

8-Cinnamyl-6-(methoxycarbonyl)-4-phenyl-2,3,4,5-tetrahydro-2,5-imino-1H-azepine (**9b**): colourless needles from hexane; mp 118–119°C; IR (KBr) ν_{max} = 3400, 1720, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 2.24 (1 H, ddd, *J* = 4.0, 4.6, and 13.2 Hz, 3-H), 2.51 (1 H, dd, *J* = 9.3 and 13.2 Hz, 3-H), 3.18 (1 H, dd, *J* = 6.9 and 13.8 Hz, >NC*H*HCH=), 3.29 (1 H, ddd, *J* = 1.3, 5.6, and 13.8 Hz, >NCH-*H*CH=), 3.48 (1 H, dd, *J* = 4.0 and 9.3 Hz, 4-H), 3.65 (3 H, s, OMe), 3.92 (1 H, s, 5-H), 4.36 (1 H, br t, *J* = 4.5 Hz, 2-H), 4.91 (1 H, br, NH), 6.33 (1 H, ddd, *J* = 5.6, 6.9 and 15.8 Hz, –C*H*=CH-Ph), 6.51 (1 H, d, *J* = 15.8 Hz, –CH=C*H*-Ph), 7.16-7.47 (11 H, ov, 7-H and Ph);

^{13}C ($CDCl_3$): δ = 46.9 (3-C), 48.5 (>N*C*H_2CH=), 50.6 (OMe), 55.7 (4-C), 63.0 (5-C), 69.3 (2-C), 100.0 (6-C), 126.6, 126.3, 127.1, 127.3, 128.2, 128.5, 137.1, 146.6 (Ph-C), 127.5 (–*C*H=CH-Ph), 131.8 (–*C*H=CH-Ph), 139.6 (7-C), 167.9 (CO_2). $C_{23}H_{24}N_2O_2$ (360.5): calcd. C, 76.64; H, 6.71; N, 7.77%; found C, 76.55; H, 6.62; N, 7.83%.

Single-crystal X-ray structure analysis of iminoazepine ***6a***. Single crystals of compound **6a** were obtained from hexane as prisms. A crystal of approximate dimensions 0.300 × 0.340 × 0.420 mm was used for data collection. All measurements were made on a Rigaku AFC5S diffractometer by employing graphite–monochromated Mo–Kα radiation. The unit–cell dimensions were obtained by least–squares analysis of 24 reflections within the range of $23.6 < 2\theta < 38.4°$. The crystal data for compound **6a** are given: crystal system: monoclinic; space group: C 1 2/c 1; cell constants: *a*: 25.64(2)Å, *b*: 8.78(1)Å, *c*: 9.428(9)Å, V: 2009(4)Å^3; β = 108.8(1)°; Z value: 8; Dc: 1.159 g cm^{-3}. The ω-2θ scan technique to a maximum 2θ-value of 55.0° was used. Scans of (1.00 + 0.30 tan θ)° were made at a speed 16° min^{-1}. A total of 2103 observed reflections (unique: 2049; R_{int} = 0.063) was collected. All calculations were performed using TEXAN program.[9] Atoms other than hydrogen were refined anisotropically. The structures were solved by direct methods (SIR)[10] and refined by least–squares to *R* 0.054 (R_w 0.057) for compound **6a**.

Received 5 July 2000; accepted 5 September 2000
Paper 00/422

References

1 For a review on vinamidines, see: D. Lloyd, H. McNab, *Angew. Chem. Int. Ed. Engl.*, 1976, **15**, 459.
2 A. Kamimura, E. Sato, D. Kanayama, M. Noguchi, unpublished data.
3 S. Takamura, T. Yoshimiya, S. Kameyama, A. Nishida, H.Yamamoto, M. Noguchi, *Synthesis*, 2000, 637.
4 This compound can be purchased from Ube Industries LTD.
5 Crystallographic data for the structure of cycloadduct **6a** have been deposited with the Cambridge Crystallographic Data Centre no. 146327. 12 Union Road, Cambridge CB2 1EZ, UK.
6 G. Büchi, J. A. Carlson, J. E. Powell, L. F. Tietze, *J. Am. Chem Soc.*, 1973, **95**, 540.
7 M. Noguchi, H. Yamada, S. Takamura, K. Okada, A. Kakehi, H. Yamamoto, *Tetrahedron*, 2000, **56**, 1299; M. Noguchi, H. Yamada, S. Takamura,T. Uchida, M. Hironaka, A. Kakehi, H. Yamamoto, *Eur. J. Org. Chem.*, 2000, 1489. Also, see references cited therein.
8 Description of usual instruments, general procedures, and chromatographic procedures have been reported.[7]
9 TEXAN–TEXRAY, Structure Analysis Package, Molecular Structures Corporation, 1985.
10 M.C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, G. Polidori, R. Spagna, D. Viterbo, *J. Appl. Crystallogr.*, 1989, **22**, 389.