SHORT PAPER

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Synthesis of 3*c*,4*r*,5*t*-1,2-dimethyl-3,5-diaryl pyrazolidine-4-carboxylic acid *via* intermolecular [3⁺+2] cycloaddition†

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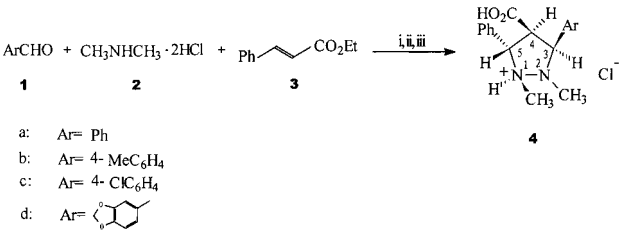
1,2-Dimethyl-3,5-diarylpyrazolidine-4-carboxylic acid derivatives **4a–d** were synthesised stereo-selectively *via* intermolecular [3⁺+2] cycloaddition of aldehydes **1a–d** and 1,2-dimethylhydrazine dihydrochloride (**2**) with ethyl *trans*-cinnamate (**3**), stereochemistries of which were assigned by ^{1}H-NOESY spectroscopy, and relative configurations confirmed by X-ray diffraction of one of them (**4a**).

Some pyrazolidines and their derivatives exhibit a broad range of biological activities or industrially useful chemical properties.[1–5] But the methods for the preparation of functional group substituted pyrazolidines have been reported rarely.[6] Banuelos *et al*.[7] have reported the preparation of functionalised pyrazolidines by the reduction of N-alkylpyrazolium salts with complex metal hydrides.[7] But some of these processes also afforded 3-pyrazolines, particularly when there was an ethoxycarbonyl group at C-4. 1,3-Dipolar cycloaddition is another valuable method for the construction of functionalized pyrazolidines.[8–10] Alternatively, [3⁺+2] cycloaddition[11–13] was proposed as a cycloaddition of cationic dipole with dipolarophile about 20 years ago, where cycloadducts were prepared conveniently under milder conditions by acid-catalysed reaction of hydrazone with dipolarophile and the deprotonation of the products. In our search for novel biologically active lead compounds, we managed to synthesise the compounds **4a–d** *via* [3⁺+2] cycloadditions of cationic dipoles [ArCH=N⁺(Me)NHMe] formed *in situ* by aldehydes **1a–d** and 1,2-dimethylhydrazine dihydrochloride (**2**) with ethyl *trans*-cinnamate (**3**) as dipolarophile, followed by hydrolysis of the adducts and hydrochlorination which made the compounds more stable in the air. (Scheme 1)

Reagents and conditions: (i), ethylene glycol, 140°C, 10h; (ii), NaOH/H_2O/EtOH, r.t, 0.5h. (iii), HOAc/H_2O, then HCl/Et_2O.



Scheme 1

The cycloadducts of the reaction isolated in this paper were 3*c*,4*r*,5*t*-1,2-dimethyl-3,5-diarylpyrazolidine-4-carboxylic acid hydrochlorides. Other isomers of cycloadducts were not detected in the NMR spectra of the reaction mixtures. So it can be seen that the cycloaddition in this paper is highly stereoselective. The structures of the products **4a–d** were established based on the elemental analyses, IR, MS, ^{1}H-NMR and ^{1}H-NOESY spectra, and the relative configurations were confirmed by X-ray diffraction of one of them (**4a**).

As the coupling constant between 3-H and 4-H is almost identical to that between 4-H and 5-H , a triplet for 4-H therefore appeared in the ^{1}H-NMR spectra for **4a–d**. In their NOESY spectra, the only strong NOE effect between 3-H and 4-H showed the 3,4-*cis* configuration. The 4,5-*trans* configurations of the products were proved by the absence of significant NOE effect between 4-H and 5-H in their NOESY spectra. Huisgen and Weinberger[14] pointed out that 1,3-dipolar cycloaddition was a stereospecific, concerted cycloaddition, and the configuration of the reactants must be retained in that process. Our observations are consistent with their inference.

The relative configurations were also confirmed by X-ray diffraction of one of them (**4a**). From Fig.1, the conformation of the pyrazolidine ring is near to an envelope with N1 out of the mean plane defined by atoms N2, C3, C4 and C5. The two phenyl rings and the pyrazolidine ring are not coplanar, the angle between the two phenyl rings being 26.66°. The carboxylic group is in *cis* and *trans* positions with respect to the 3-phenyl and 5-phenyl groups, respectively. Furthermore, the 1,5-*trans* relationship of 1-CH_3 and 5-Ph can also be observed from Fig.1, which accords with the demand of molecular lowest energy conformation.

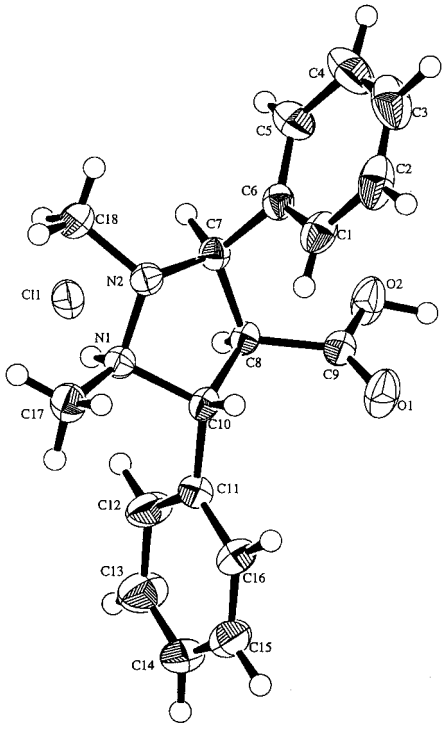


Fig. 1 X-Ray crystal structure of compound 4a.

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

In conclusion, the 3*c*,4*r*,5*t*-1,2-dimethyl-3,5-diarylpyrazolidine-4-carboxylic acid derivatives **4a**–**d** have been synthesised stereoselectively *via* intermolecular [3$^+$+2] cycloaddition for the first time, and their 3,4-*cis*, 4,5-*trans* stereochemistry is determined.

Experimental

Melting points were determined on a Yanaco melting point apparatus. IR spectra were measured on a Shimadzu IR400 spectrometer with KBr pellets. ^{1}H-NMR and NOESY were recorded on a Bruker ACF-300 instrument with DMSO-d_6 and D_2O as solvent and TMS as an internal standard. The *J* values are given in Hz. Elemental analyses were performed on a Perkin-Elmer 240C instrument. Mass spectra were recorded on a Finnigan FTMS-2000 instrument with 70eV. The X-ray diffraction was made on a Rigaku RAXIS-IV diffractometer with graphite monochromated Mo–Kα radiation.

General procedure for the preparation of 3c,4r,5t-*1,2-dimethyl-3,5-diaryl pyrazolidine-4-carboxylic acid hydrochloride* **4a–d**: A mixture of aldehyde **1** (5 mmol), 1,2-dimethylhydrazine dihydrochloride **2** (5 mmol), and ethyl *trans*-cinnamate **3** (50 mmol) was heated in ethylene glycol (20 ml) at 140 °C for 10 h under nitrogen. After the mixture was cooled to room temperature, triethylamine (10 mmol) was added to the reaction mixture, and the mixture was further stirred for 0.5h, then poured into a large amount of water and extracted with chloroform (3 × 20 ml), dried over anhydrous sodium sulfate. After evaporation of the chloroform and an excess amount of ethyl *trans*-cinnamate, the residue was dissolved in ethanol (20 ml), 10 ml of 10%NaOH aq. added, then the mixture was stirred for 0.5h at room temperature. After the solvent was evaporated under reduced pressure, the residue was dissolved in water (30 ml), then filtered, the filtrate was acidified with HOAc aq. and extracted with ether (3 × 20 ml), dried over anhydrous sodium sulfate. After the treatment with dry HCl gas saturated ether, the white precipitate was recrystallized from chloroform–petroleum ether to give products **4a–d.**

3c,4r,5t-*1,2-dimethyl-3,5-diphenylpyrazolidine-4-carboxylic acid hydrochloride* **4a**: This compound was obtained as colorless grains in 31% yield, mp 253–254°C (dec.) (Found: C, 65.0; H, 6.5; N, 8.2. $C_{18}H_{21}ClN_2O_2$ requires C, 64.9; H, 6.4; N, 8.4%); υ_{max}/cm^{-1} 2888, 2656, 2567 (HN$^+$), 1731 (CO), 1458, 1226, 1193; δ_H (ppm) 2.77 (3H, s, N2–CH$_3$), 2.87 (3H, s, N1–CH$_3$), 4.04 (1H, t, *J* 10.6, C4-H), 4.81 (1H, d, *J* 10.8, C3–H), 4.99 (1H, d, *J* 10.2, C5–H), 7.41–7.54 (10H, m, 3,5–PhHs); *m/z* (%) 296 (M$^+$-HCl, 37), 281(15), 235 (24), 147 (100).

3c,4r,5t-*1,2-dimethyl-3-(4-methylphenyl)-5-phenylpyrazolidine-4-carboxylic acid hydrochloride* **4b**: This compound was obtained as white crystals in 27% yield, mp 241°C (dec.) (Found: C, 65.9; H, 6.6; N, 8.1. $C_{19}H_{23}ClN_2O_2$ requires C, 65.8; H, 6.6; N, 8.1%); υ_{max}/cm^{-1} 2887, 2638, 2566 (HN$^+$), 1736 (CO), 1461, 1410, 1269, 1188; δ_H (ppm) 2.22 (3H, s, C–CH$_3$), 2.68 (3H, s, N2–CH$_3$), 2.80 (3H, s, N1–CH$_3$), 3.89 (1H, t, *J* 10.3, C4–H), 4.72 (1H, d, *J* 10.8, C3–H), 4.78 (1H, d, *J* 9.9, C5–H), 7.16–7.28 (4H, m, C3–ArHs), 7.44–7.49 (5H, m, C5–PhHs); *m/z* (%) 310 (M$^+$-HCl, 84), 295 (31), 249 (21), 207 (13), 161 (100), 147 (86).

3c,4r,5t-*1,2-dimethyl-3-(4-chlorophenyl)-5-phenylpyrazolidine-4-carboxylic acid hydrochloride* **4c**: This compound was obtained as white crystals in 17% yield, mp 249–250 °C (dec.) (Found: C, 59.1; H, 5.3; N, 7.5. $C_{18}H_{20}Cl_2N_2O_2$ requires C, 58.9; H, 5.5; N, 7.6%); υ_{max}/cm^{-1} 2890, 2635 (HN$^+$), 1735 (CO), 1461, 1410, 1188; δ_H (ppm) 2.63 (3H, s, N2–CH$_3$), 2.81 (3H, s, N1–CH$_3$), 3.99 (1H, t, *J* 10.1, C4–H), 4.69 (1H, d, *J* 10.2, C3–H), 4.82 (1H, d, *J* 9.6, C5–H), 7.34–7.48 (9H, m, C3–ArHs and C5–PhHs); *m/z* (%) 330 (M$^+$–HCl, 88), 315 (37), 269 (25), 227 (9), 181 (100), 147 (96).

3c,4r,5t-*1,2-dimethyl-3-(3,4-methylenedioxyphenyl)-5-phenylpyrazolidine-4-carboxylic acid hydrochloride* **4d**: This compound was obtained as white grains in 25% yield, mp 252–253 °C (dec.) (Found: C, 60.8; H, 5.6; N, 7.3. $C_{19}H_{21}ClN_2O_4$ requires C, 60.6; H, 5.6; N, 7.4%); υ_{max}/cm^{-1} 2894, 2634, 2552 (HN$^+$), 1736 (CO), 1250, 1185; δ_H (ppm) 2.68 (3H, s, N2–CH$_3$), 2.82 (3H, s, N1–CH$_3$), 3.93 (1H, t, *J* 10.3, C4–H), 4.65 (1H, d, *J* 10.7, C3–H), 4.80 (1H, d, *J* 9.8, C5–H), 5.88 (2H, s, -OCH$_2$O-), 6.80–6.90 (3H, m, C3–ArHs), 7.42–7.51 (5H, m, C5–PhHs); *m/z* (%) 340 (M$^+$-HCl, 100), 325 (12), 279 (9), 237 (7), 191 (75), 147 (54).

Crystal data for compound **4a**: $C_{18}H_{21}ClN_2O_2$, Fw=332.83, F(000)=704.00, colorless crystal, orthorhombic system, *a* = 12.840(2), *b* = 17.721(2), *c* = 7.642(4), V = 1738.6899 Å,^{3} space group $P2_12_12_1$(#19), Z=4, d_c = 1.271g cm^{-3}, μ (MoKα) =2.30 cm^{-1}.

The intensity data were collected on a Rigaku RAXIS-IV diffractometer with graphite monochromated Mo–Kα radiation (λ = 0.71070 Å) and ω –2 θ scan technique [*T* = 291(1)K; 2 θ_{max} = 55.0°].

The structure was solved by direct methods[15] and expanded using Fourier techniques.[16] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically. The final cycle of full-matrix least-squares refinement was based on 1740 observed reflections *[I*>3.00 σ (*I)]* and 275 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of $R = 0.036$ and $R_w = 0.046$.

Neutral atom scattering factors were taken from Cromer and Waber.[17] Anomalous dispersion effects were included in F_{calc},[18] the values for Δf′ and Δf″ were those of Creagh and McAuley,[19] the values for the mass attenuation coefficients are those of Creagh and Hubble.[20] All calculations were performed using the teXsan[21] crystallographic software package of Molecular Structure Corporation.

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