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Rapid and efficient synthesis of optically active pyrazoles under solvent-free conditions

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Abstract—2-Formyl glycals undergo rapid condensation with arylhydrazines under solvent-free conditions to give the corresponding optically pure 4-substituted pyrazoles in good yields with high selectivity. The stereochemistry of the products was assigned by various NMR experiments.
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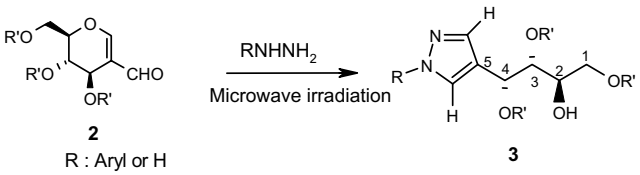
Microwave-assisted reactions have attracted much interest because of the simplicity of operation and mild reaction conditions. Salient features of the microwave approach are improved yields, enhanced reaction rates, formation of pure products in high yields and ease of isolation. Solvent-free microwave assisted reactions have gained more popularity as they provide an opportunity to work with open vessels.[1,2] The pyrazole unit is the core structure in a number of natural products.[3] Many pyrazole derivatives are known to exhibit a wide range of biological properties such as anti-hyperglycemic, analgesic, anti-inflammatory, anti-pyretic, anti-bacterial, hypoglycemic and sedative–hypnotic activity.[4] Particularly, arylpyrazoles are important in medicinal and pesticidal chemistry.[5] Recently, some arylpyrazoles were reported to have non-nucleoside HIV-1 reverse transcriptase inhibitory activity.[6] Extensive studies have been devoted to arylpyrazole derivatives such as Celecoxib, a well-known cyclooxygenase-2 inhibitor.[7] Thus continuing efforts have been made to develop more general and versatile synthetic methods for the synthesis of pyrazoles.

In this article, we wish to report a novel and rapid method for the synthesis of a new class of optically pure 4-substituted pyrazoles from 2-formyl glycals and arylhydrazines. Thus, treatment of 3,4,6-tri-*O*-ethyl-2-*C*-formyl-D-glucal[8] with phenylhydrazine under microwave irradiation and solvent-free conditions afforded 1,3,4-triethoxy-4-(1-phenyl-1*H*-4-pyrazolyl)-(2*R*,3*S*,4*R*)-butan-2-ol **3a** in 83% yield. In a similar manner reaction of 3,4,6-tri-*O*-benzyl-2-*C*-formyl-D-glucal[8] and phenylhydrazine gave the corresponding pyrazole **3c** in 85% yield (Scheme 1).

A variety of arylhydrazines such as *p*-chloro, *p*-methoxy, *m*-chloro and *o*-ethyl derivatives reacted efficiently with 3,4,6-tri-*O*-benzyl-2-*C*-formyl-D-glucal[8] under microwave irradiation to afford the corresponding pyrazoles in good yields (entries e–h, Table 1).[9] Like arylhydrazines, hydrazine hydrate itself also afforded the respective pyrazoles in good yields (entries d and j, Table 1). Other substrates such as 3,4,6-tri-*O*-methyl-2-*C*-formyl-D-glucal[8] gave 4-substituted pyrazoles under similar conditions. The reactions were carried out both under microwave as well as thermal conditions. The reaction



2
R : Aryl or H
R' : Bn, Et, Me

3

Scheme 1.

Keywords: Arylhydrazines; 2-Formyl glycals; Microwaves; Pyrazoles.
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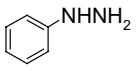
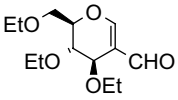
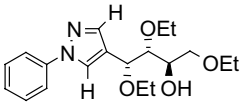
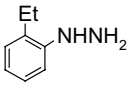
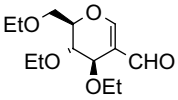
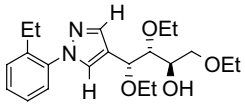
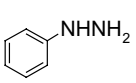
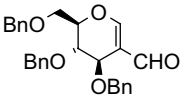
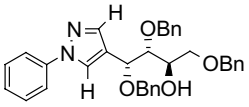
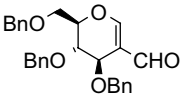
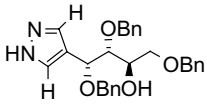
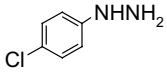
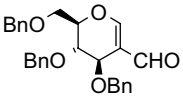
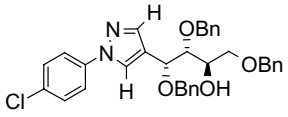
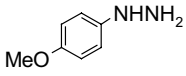
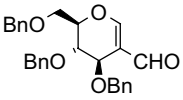
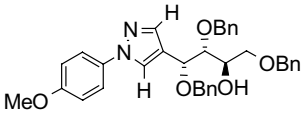
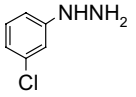
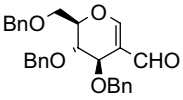
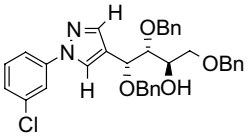
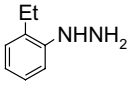
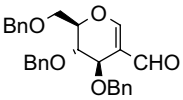
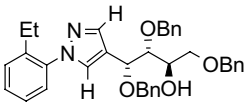
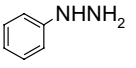
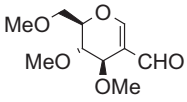
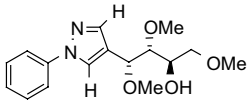
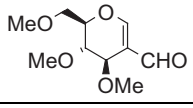
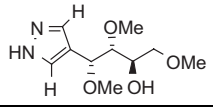
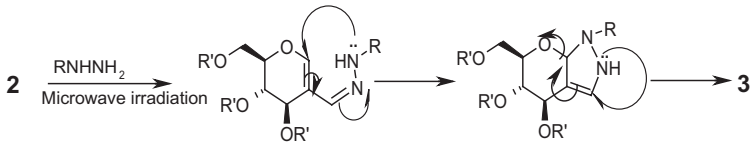
Table 1. Microwave-promoted synthesis of pyrazoles[11] from 2-formyl glycals and arylhydrazines

Entry	Arylhydrazine **1**	2-Formyl glycal **2**	Product[a] **3**	Reaction time	Yield (%)[b]
a				5 min (8.5 h)[c]	83 (78)[c]
b				4 min (9.0 h)	81 (75)
c				5 min (8.0 h)	85 (76)
d	$NH_2NH_2{\cdot}H_2O$			3 min (6.0 h)	87 (80)
e				6 min (9.0 h)	82 (69)
f				5 min (7.5 h)	86 (73)
g				6 min (8.0 h)	79 (65)
h				5 min (8.5 h)	82 (70)
i				4 min (9.0 h)	81 (67)
j	$NH_2NH_2{\cdot}H_2O$			3 min (6.5 h)	85 (72)

[a] Products were characterized by ^1H NMR, ^{13}C NMR, IR and mass spectroscopy.
[b] Yields refers to pure products after chromatography.
[c] Time and yield reported in parenthesis were obtained under conventional heating.

temperature was controlled using a pulsed irradiation technique (1 min with 20 s intervals) and the temperature was measured after each pulse. The lowest observed temperature was 80 °C after irradiation for 1 min at 450 W and the highest temperature was 110 °C after irradiation for 3 min at the same power. The reaction rates and yields were dramatically enhanced by microwave irradiation. The rate enhancement under microwave irradiation can be attributed to the absorption of more microwave energy by the polar reactants, which generates sufficient heat energy to promote the reaction. The same reaction, under thermal conditions, at 90 °C took 6–9 h to achieve complete conversion. Probably the reaction proceeds through the in situ formation of a hydrazone and subsequent cyclization followed by intramolecular pyran ring opening results in the formation of the pyrazole (Scheme 2).

The structure of the product **3a** was assigned by using various solution NMR experiments such as DQCOSY, NOESY, HSQC and HMBC. The HSQC spectrum showed the presence of 10 CH's, 4 CH_2's and 3 CH_3's. The appearance of NOE cross peaks between H3/H5, H5/H8, H7/H8 indicated and the existence of a pyrazole five membered ring involving the C5, C6 and C7 carbons. The heteronuclear correlation (HMBC) between



Scheme 2.

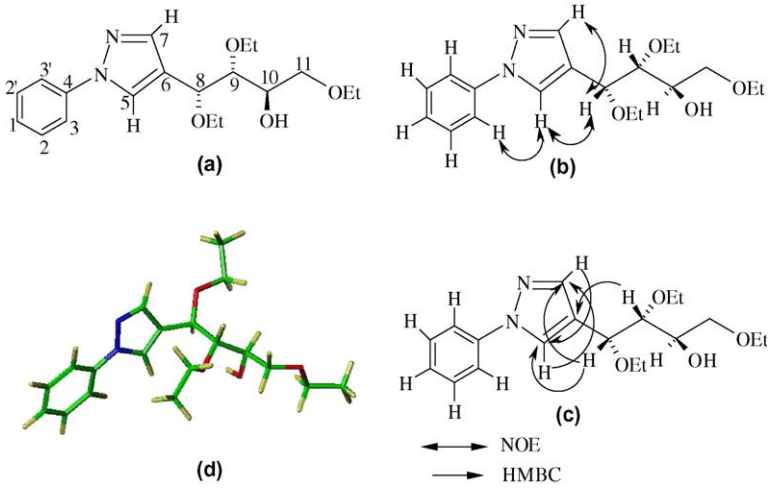


Figure 1. Chemical structure and numbering used in NMR assignments: (a) NOE cross peaks; (b) diagram, heteronuclear correlations; (c) and energy minimized structure;[10] (d) of compound **3a**.

H5/C7, H7/C5, H8/C5, H8/C7, and H9/C6 further supported the pyrazole structure (Fig. 1).

The HSQC spectrum of **3c** showed the presence of 10 CH's and 4 CH_2's as well as the phenyl group. The NOE cross peaks between H3/H5, H5/H8, H7/H8 and heteronuclear correlations (HMBC) between H5/C7, H7/C5, H8/C5, H8/C7 and H9/C6 strongly support the structure of the substituted pyrazole.

In conclusion, we have described a rapid and efficient protocol for the synthesis of enantiomerically pure pyrazoles from 2-formyl glycals and arylhydrazines using microwave irradiation under solvent-free conditions. The present method is a very useful process for the preparation of highly functionalized pyrazole derivatives in a one-pot operation. The reduced reaction times together with the minimization of thermal decomposition of the products are the main advantages of microwave heating; further improvements may be possible using a continuous microwave reactor.

Acknowledgements

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8. The starting 2-formyl glycals were prepared according to the procedure reported in the literature: Ramesh, N. G.; Balasubramanian, K. K. *Tetrahedron Lett.* **1991**, *32*, 3875–3878.
9. *General procedure*: A mixture of 2-formyl glycal (1 mmol) and arylhydrazine (1.2 mmol) was subjected to microwave irradiation using a BPL, BMO-800T domestic oven operated at 450 W for the appropriate time (see Table 1). After complete conversion as indicated by TLC, the reaction mixture was quenched with water and extracted with ethyl acetate (2 × 10 mL). The combined organic

layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) to afford the corresponding optically active 4-substituted pyrazole in pure form.

10. Molecular mechanics calculations were carried out using the Sybyl 6.8 programme on a Silicon graphics O2 workstation.
11. Compound **3a**: Liquid, $[\alpha]_D^{27}$ −8.3 (*c* 1.0, $CHCl_3$), IR (KBr): *v* 3470, 2973, 1600, 1503, 1399, 1218, 1095, 765, 690 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) : δ 7.95 (s, 1H, *H*5), 7.68 (s, 1H, *H*7), 7.68 (dt, *J* = 1.2, 7.4 Hz, 2H, *H*3 and *H*3′), 7.43 (dt, *J* = 1.2, 7.4 Hz, 2H, *H*2 and *H*2′), 7.26 (tt, *J* = 1.2, 7.4 Hz, 1H, *H*1), 4.72 (d, *J* = 3.1 Hz, 1H, *H*8), 3.92 (ddd, *J* = 3.4, 5.0, 7.7 Hz, 1H, *H*10), 3.63–3.39 (m, 6H, 3OCH_2's), 3.40 (dd, *J* = 3.1, 5.0, 1H, *H*9), 3.50 (m, 1H, *H*11), 3.42 (m, 1H, *H*11′), 1.22 (t, *J* = 7.0 Hz, 3H, *Me*), 1.22 (t, *J* = 7.0 Hz, 3H, *Me*), 1.14 (t, *J* = 7.0 Hz, 3H, *Me*). ^{13} C NMR, proton decoupled, $CDCl_3$: δ 140.6, 139.8, 129.4, 126.2, 125.4, 121.8, 118.7, 81.5, 73.8, 71.3, 70.0, 67.8, 66.7, 65.0, 15.6, 15.2, 15.1. EIMS *m*/*z*: 349 (M^+ + 1, 10), 259 (5), 230 (20), 201 (100), 173 (80), 141 (20), 105 (45), 77 (30); HRMS calcd for $C_{19}H_{28}N_2O_4$: 349.2127, found: 349.2114. Compound **3c**: liquid, $[\alpha]_D^{27}$ − 26.9 (*c* 1.3, $CHCl_3$), IR (KBr): *vv* 3417, 2976, 1600, 1501, 1489, 1392, 1217, 1071, 752, 697 cm^{-1}. (^1H NMR, 500 MHz, $CDCl_3$): δ 7.87 (s, 1H, *H*5), 7.69 (s, 1H, *H*7), 7.61 (dd, *J* = 1.3, 7.4 Hz, 2H, *H*3 and *H*3′), 7.43 (dt, *J* = 1.3, 7.4 Hz, 2H, *H* 2, *H*2′), 7.34–7.17 (m, 15H, aromatic), 7.28 (tt, *J* = 1.3, 7.4 Hz, 1H, *H*1), 4.77 (d, *J* = 3.8 Hz, 1H, *H*8), 4.60–4.35 (m, 6H, 3OCH_2's), 4.01 (m, 1H, *H*10), 3.71 (dd, *J* = 3.8, 6.8 Hz, 1H, *H*9), 3.62 (dd, *J* = 4.0, 13.5 Hz, 1H, *H*11), 3.60 (dd, *J* = 5.1, 13.5 Hz, 1H, *H*11′), 2.80 (br s, 1H, OH). ^{13}C NMR, proton decoupled, $CDCl_3$: δ 140.7, 140.0, 138.0, 137.9, 137.7, 129.4, 129.4, 128.5, 128.5, 128.4, 128.4, 128.3, 128.3, 128.2, 128.2, 128.11, 128.1, 127.9,127.9, 127.8, 127.7, 127.7, 126.4, 126.3, 121.0, 118.9, 118.9, 81.4, 74.5, 73.4, 73.1, 71.0, 70.9, 70.3. FABMS *m*/*z*: 535 (M^+ + 1, 10), 427 (15), 367 (5), 293 (12), 277 (25), 263 (20), 109 (30), 91 (80), 79 (40), 69 (70), 55 (100); HRMS calcd for $C_{34}H_{34}N_2O_4$: 535.2596, found: 535.2581 (note: similar ^{13}C values correspond to two carbon atoms).