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A facile synthesis of *N*-substituted 2,5-dimethylpyrroles with saccharin as a green catalyst

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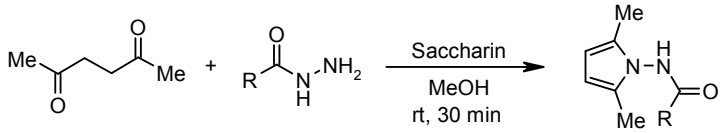

The paper describes a convenient method for the preparation of *N*-substituted 2,5-dimethylpyrroles using edible sweetener saccharin. Various heterocyclic and aromatic hydrazides have been converted to their corresponding Paal–Knorr pyrroles at room temperature in methanol with saccharin as a green catalyst. Saccharin can be recycled for the next two runs without apparent loss in its activity. Here we propose a method which is speedy, proficient, and ecologically safe.

Keywords: pyrrole, saccharin, cyclocondensation, Paal–Knorr reaction.

The ring closure reaction between amines or hydrazides and open chain carbonyl compounds forms compounds of a class called Paal–Knorr pyrroles. Pyrroles are the synthons of quite a few unnatural heterocyclic derivatives that demonstrate properties like antimicrobial,[1–3] antitubercular,[4–6] analgesic,[7–9] anti-inflammatory,[10–12] and antitumor activities.[13–15] Pyrrole ring is the key structural unit of important naturally occurring compounds, such as vitamin B12, heme, and chlorophyll.

The popular Paal–Knorr pyrrole synthesis has been originally carried out by boiling amines in acetic acid for an elongated period.[16] There are different promoting agents in use like $Sc(OTf)_3$,[17] xanthan sulfuric acid,[18] silica sulfuric acid,[19] *p*-toluenesulfonic acid,[20] amberlite IR 120 acidic resin,[21] polystyrene-supported $GaCl_3$,[22] silica-supported $SbCl_3$,[23] PEG-bound sulfonic acid,[24] montmorillonite.[25] Although there are a number of catalysts and different synthetic strategies[26–28] the application of the Paal–Knorr synthesis is limited by the harsh reaction conditions and wearying work-up.

Most of the methods are particular to certain types of starting materials. Thus, we faced a difficulty in the reaction of hexane-2,5-dione (**1**) with 1-(4-fluorophenyl)-1,3-dihydro-2-benzofuran-5-carbohydrazide (**2a**).[29] Gentle reaction conditions were required to obtain the desired 1-(4-fluorophenyl)-*N*-(2,5-dimethyl-1*H*-pyrrol-1-yl)-1,3-dihydro-2-benzofuran-5-carboxamide (**3a**) (Scheme 1). Compounds **2a** and **3a** can be regarded as derivatives of 1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile[29] which has been used as an intermediate in the synthesis of citalopram,[30] a well-known antidepressant.[31–36]

Natural sugars and unnatural sweeteners are becoming employed as reagents and catalysts in organic functional group transformations. Recently, β-cyclodextrin,[37] a cyclic oligosaccharide containing seven glucose units in the molecule has been introduced as a catalyst for the Paal–Knorr reaction. In search of a green catalyst, we have come across the artificial sweetener saccharin. Saccharin (1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide) is a Brønsted acid with moderate acidity (pK_a 2.32). This inexpensive, edible, and benign chemical has been used as a catalyst for some organic functional group transformations.[38,39] To the best of our knowledge, a saccharin-mediated Paal–Knorr reaction has not been demonstrated yet. In continuance to our work on development of new reagents in organic synthesis,[40,41] we herewith report a simple method to produce pyrroles using saccharin as an interesting catalyst.

The purpose of the present work was to obtain 1-(4-fluorophenyl)-*N*-(2,5-dimethyl-1*H*-pyrrol-1-yl)-1,3-dihydro-2-benzofuran-5-carboxamide (**3a**) from 1-(4-fluorophenyl)-1,3-dihydro-2-benzofuran-5-carbohydrazide (**2a**). To develop an easily adaptable catalytic version of the Paal–Knorr pyrrole synthesis was another objective of the investigation. Firstly, the solubility of compound **2a** was tested in a variety of solvents. Compound **2a** was soluble in methanol, but only sparingly soluble in other polar solvents like water, ethanol, and isopropanol. Similarly, it was soluble in diethyl ether, but hardly soluble in toluene, ethyl acetate, hexane, and dichloromethane. As diethyl ether is a highly volatile flammable liquid, methanol was chosen as the reaction medium.

We carried out the reaction of compounds **1** and **2a** in methanol at various temperatures. Without the use of any

Scheme 1

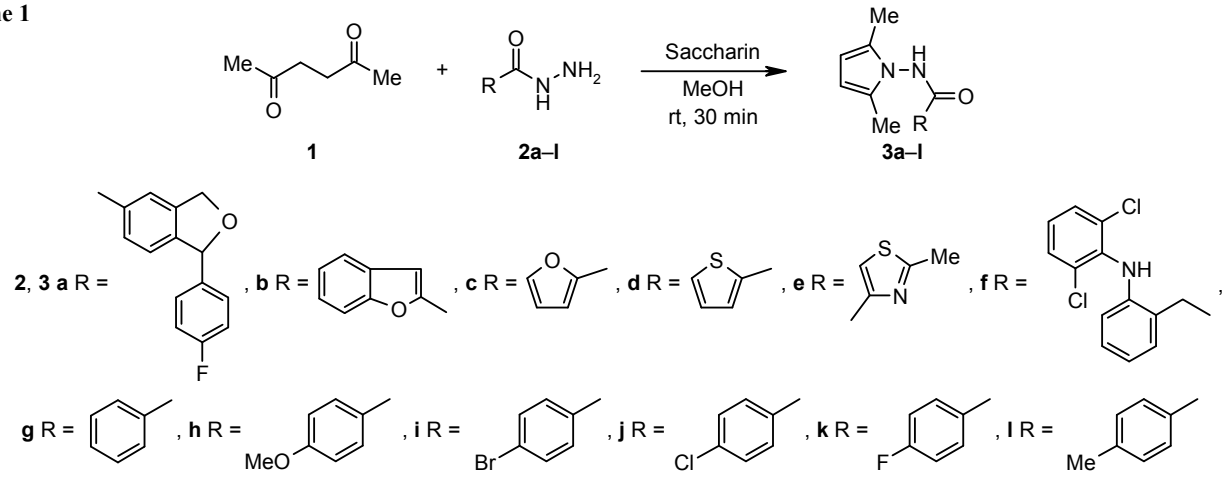

Table 1. Effect of different catalysts on the synthesis of compound **3a***

Entry	Catalyst	pK_a	Yield, %
1	*p*-Toluenesulfonic acid	–2.8	0
2	Benzenesulfonic acid	–2.8	0
3	Methanesulfonic acid	–1.9	0
4	Sulfamic acid	1.0	29
5	Oxalic acid	1.2	51
6	Saccharin	2.3	86
7	Citric acid	3.1	71
8	Glycolic acid	3.8	63
9	Acetic acid	4.7	36

* Reaction conditions: compound **1** (6.0 mmol), compound **2a** (4.0 mmol), catalyst (1.0 mmol), MeOH (6 ml), room temperature, 30 min.

Table 2. Effect of the relative amount of saccharin on the yield of compound **3a***

Entry	Amount of saccharin, mol %	Yield, %
1	12.5	53
2	25	86
3	37.5	86
4	50	86

* Reaction conditions as specified in Table 1.

Table 3. Melting points and yields of synthesized compounds **3a–l**

Compound	Mp, °C	Yield, %	Compound	Mp, °C	Yield, %
3a	182–184	86	**3g**[42]	164–166	84
3b	186–188	82	**3h**[42]	200–202	92
3c	194–196	89	**3i**	208–210	85
3d	214–216	91	**3j**	196–200	87
3e	210–212	80	**3k**	190–192	90
3f	218–220	84	**3l**	174–176	90

catalyst, the reaction did not go to completion. The use of a catalyst was, therefore, an obvious necessity. In order to find the best conditions for the reaction under investigation, we tried to prepare compound **3a** using several Brønsted acids acting as catalysts. The results are summarized in Table 1. The Paal–Knorr reaction with *p*-TsOH, benzenesulfonic acid, and methanesulfonic acid with the similar acidity yielded a complex mixture as was evident by NMR analysis. Different Brønsted acids with pK_a 1.2–3.8 afforded good to moderate yields. Saccharin with pK_a 2.3 showed the best result, and was thus chosen for further study.

The impact of the relative saccharin concentration on the model reaction was also investigated. The best catalyst load was turned out to be 25 mol % (Table 2). Lower amount of saccharin afforded lower yields while higher amounts did not cause an increase of the yield. Meanwhile, no substantial loss of the product yield was observed when the catalyst contained in the filtrate from the reaction mixture was reused twice.

To appreciate the scope of the saccharin-mediated Paal–Knorr reaction, different hydrazides **2b–l** were condensed with hexane-2,5-dione (**1**) under the optimized conditions (Scheme 1). The yields of the corresponding products **3b–l** are shown in Table 3. A close inspection of the yields shows that heterocyclic, as well as aromatic hydrazides react equally well with hexane-2,5-dione (**1**) under the described conditions forming stable products.

In conclusion, there are several reports in literature describing the use of catalysts for the Paal–Knorr condensation. In the present work, saccharin exhibited a promising applicability owing to its non-toxic nature, low cost, ecological safety, product yield, easy isolation procedures, and reusability.

Experimental

Fourier transform IR spectra in KBr pellets were recorded on a Shimadzu 8300 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra (400 and 100 MHz) were recorded on a Bruker AM spectrometer in DMSO-d_6 solution with TMS as internal standard. ESI mass spectra were recorded on an Agilent 6520 ESIQTOF instrument at ionization potential of 110 V and acetonitrile as solvent. Elemental analyses

were performed on a Vario-EL instrument. The melting points were determined on a Thomas Hoover apparatus and remain uncorrected. Reactions were monitored by thin-layer chromatography using 0.25 mm silica gel plates ($60F_{254}$, Merck) and PhMe–EtOAc, 2:1, as the mobile phase. Visualization was made with ultraviolet light. Reagents were obtained commercially and used as received.

Saccharin-mediated Paal–Knorr pyrrole cyclocondensation (General method). Saccharin (0.183 g, 1.0 mmol) was added to a solution of hexane-2,5-dione (**1**) (0.684 g, 6.0 mmol) and hydrazide **2a–l** (4.0 mmol) in methanol (6 ml). The mixture was stirred at room temperature for 30 min. After the completion of the reaction, the mixture was cooled in an ice bath. The brown solid product was filtered off and recrystallized from MeOH. The filtrate could be used for the next two runs with fresh reactants **1** and **2a–l** without any sign of decreased catalytic activity.

1-(4-Fluorophenyl)-*N*-(2,5-dimethyl-1*H*-pyrrol-1-yl)-1,3-dihydro-2-benzofuran-5-carboxamide (3a). IR spectrum, ν, cm^{-1}: 3251 (NH), 2356 (Ar CH), 1662 (C=O), 1512 (CH_3), 1330 (COC), 1226 (CF). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.25 (1H, s, NH); 7.94 (1H, s, H Ar); 7.84 (1H, d, *J* = 7.6, H Ar); 7.42 (2H, t, *J* = 6.8, H Ar); 7.21 (3H, t, *J* = 8.8, H Ar); 6.26 (1H, s, CH); 5.70 (2H, s, H pyrrole); 5.36 (1H, d, *J* = 12.8, CH); 5.18 (1H, d, *J* = 12.8, CH); 2.20 (6H, s, $2CH_3$). ^{13}C NMR spectrum, δ, ppm: 166.2; 163.4; 146.4; 139.9; 138.8; 132.2; 129.1; 129.0; 127.4; 122.8; 121.3; 115.7; 103.6; 84.5; 72.8; 11.4. Mass spectrum, *m/z* (I_{rel}, %): 351 $[M+H]^+$ (100), 241 (2), 214 (10), 165 (11), 94 (20), 67 (7). Found, %: C 71.92; H 5.40; N 8.05. $C_{21}H_{19}FN_2O_2$. Calculated, %: C 71.98; H 5.47; N 8.00.

***N*-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-1-benzofuran-2-carboxamide (3b)**. IR spectrum, ν, cm^{-1}: 3232 (NH), 2993 (Ar CH), 1674 (C=O), 1589 (CH_3), 1222 (COC). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.60 (1H, s, NH); 7.84 (1H, d, *J* = 7.6, H benzofuran); 7.78 (1H, s, H benzofuran); 7.73 (1H, d, *J* = 8.0, H benzofuran); 7.56–7.52 (1H, t, *J* = 7.6, H benzofuran); 7.41–7.37 (1H, t, *J* = 7.6, H benzofuran); 5.72 (2H, s, H pyrrole); 2.05 (6H, s, $2CH_3$).^{13}C NMR spectrum, δ, ppm: 158.1; 155.0; 147.1; 128.0; 127.5; 127.2; 124.5; 123.5; 112.4; 111.8; 103.8; 11.5. Found, %: C 70.88; H 5.51; N 11.09. $C_{15}H_{14}N_2O_2$. Calculated, %: C 70.85; H 5.55; N 11.02.

***N*-(2,5-Dimethyl-1*H*-pyrrol-1-yl)furan-2-carboxamide (3c)**. IR spectrum, ν, cm^{-1}: 3217 (NH), 2354 (Ar CH), 1650 (C=O), 1522 (CH_3). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.28 (1H, s, NH); 7.79 (2H, d, *J* = 4.6, H furan); 7.17 (1H, t, *J* = 4.0, H furan); 5.72 (2H, s, H pyrrole); 2.07 (6H, s, $2CH_3$). ^{13}C NMR spectrum, δ, ppm: 162.1; 140.2; 136.8; 135.6; 112.7; 106.2; 103.5; 11.4. Found, %: C 64.62; H 5.75; N 13.77. $C_{11}H_{12}N_2O_2$. Calculated, %: C 64.69; H 5.92; N 13.72.

***N*-(2,5-Dimethyl-1*H*-pyrrol-1-yl)thiophene-2-carboxamide (3d)**. IR spectrum, ν, cm^{-1}: 3236 (NH), 2360 (Ar CH), 1674 (C=O), 1539 (CH_3). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.30 (1H, s, NH); 7.92 (2H, d, *J* = 4.8, H thiophene); 7.25 (1H, t, *J* = 4.0, H thiophene); 5.70 (2H, s, H pyrrole); 2.00 (6H, s, $2CH_3$). ^{13}C NMR spectrum, δ, ppm: 161.0; 132.8; 129.9; 128.7; 127.6; 127.5; 103.7; 11.5. Found, %: C 59.93; H 5.40; N 12.76. $C_{11}H_{12}N_2OS$. Calculated, %: C 59.97; H 5.49; N 12.72.

***N*-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-2-methyl-1,3-thiazole-4-carboxamide (3e)**. IR spectrum, ν, cm^{-1}: 3241 (NH), 2955 (Ar CH), 1612 (C=O), 1537 (CH_3). ^{1}H NMR spectrum, δ, ppm: 11.18 (1H, s, NH); 7.12 (1H, s, H thiazole); 5.61 (2H, s, H pyrrole); 2.05 (6H, s, $2CH_3$); 1.21 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 158.3; 138.3; 137.2; 135.6; 128.7 (C9); 104.1; 21.4; 11.2. Found, %: C 56.19; H 5.50; N 17.88. $C_{11}H_{13}N_3OS$. Calculated, %: C 56.15; H 5.57; N 17.86.

2-{2-[(2,6-Dichlorophenyl)amino]phenyl}-*N*-(2,5-dimethyl-1*H*-pyrrol-1-yl)acetamide (3f). IR spectrum, ν, cm^{-1}: 3328 (NH), 2360 (Ar CH), 1674 (C=O), 1450 (CH_3), 775 (CCl). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.09 (1H, s, NH); 7.71 (1H, s, H Ar); 7.52 (2H, d, *J* = 7.6, H Ar); 7.31 (1H, d, *J* = 6.0, H Ar); 7.18 (1H, t, *J* = 7.2, H Ar); 7.08 (1H, d, *J* = 6.8, H Ar); 6.92 (1H, d, *J* = 6.4, H Ar); 6.32 (1H, d, *J* = 7.2, H Ar); 5.63 (2H, s, H pyrrole); 3.78 (2H, s, CH_2); 2.06 (6H, s, $2CH_3$). ^{13}C NMR spectrum, δ, ppm: 171.5; 143.2; 137.4; 130.8; 130.0; 129.6; 128.1; 127.9; 127.1; 125.8; 124.9; 121.5; 116.7; 104.7; 103.5; 37.5; 11.6. Found, %: C 61.8; H 4.99; N 10.80. $C_{20}H_{19}Cl_2N_3O$. Calculated, %: C 61.86; H 4.93; N 10.82.

***N*-(2,5-Dimethyl-1*H*-pyrrol-1-yl)benzamide (3g)**. IR spectrum, ν, cm^{-1}: 3148 (NH), 2576 (Ar CH), 1681 (C=O), 1511 (CH_3). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.41 (1H, s, NH); 8.18 (2H, d, *J* = 7.5, H Ar); 7.61 (1H, t, *J* = 7.2, H Ar); 7.56 (2H, t, *J* = 7.6, H Ar); 5.21 (2H, s, H Pyrrole); 2.04 (6H, s, $2CH_3$). ^{13}C NMR spectrum, δ, ppm: 167.8; 136.4; 133.9; 131.0; 130.2; 128.6; 102.8; 11.1. Found, %: C 72.81; H 6.57; N 13.05. $C_{13}H_{14}N_2O$. Calculated, %: C 72.87; H 6.59; N 13.07.

4-Methoxy-*N*-(2,5-dimethyl-1*H*-pyrrol-1-yl)benzamide (3h). IR spectrum, ν, cm^{-1}: 3232 (NH), 2846 (Ar CH), 1644 (C=O), 1564 (CH_3), 1248 (COC). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.06 (1H, s, NH); 7.20 (2H, d, *J* = 8.0, H Ar); 6.92 (2H, d, *J* = 8.0, H Ar); 5.70 (2H, s, H pyrrole); 3.21 (3H, s, OCH_3); 2.03 (6H, s, $2CH_3$). ^{13}C NMR spectrum, δ, ppm: 171.4; 166.2; 134.2; 131.3; 130.1; 129.5; 103.7; 55.6; 11.1. Found, %: C 68.78; H 6.66; N 11.42. $C_{14}H_{16}N_2O_2$. Calculated, %: C 68.83; H 6.60; N 11.47.

4-Bromo-*N*-(2,5-dimethyl-1*H*-pyrrol-1-yl)benzamide (3i). IR spectrum, ν, cm^{-1}: 3144 (NH), 2972 (Ar CH), 1654 (C=O), 1502 (CH_3), 511 (CBr). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.02 (1H, s, NH); 7.86 (2H, d, *J* = 7.5, H Ar); 7.72 (2H, d, *J* = 7.5, H Ar); 5.61 (2H, s, H pyrrole); 2.02 (6H, s, $2CH_3$). ^{13}C NMR spectrum, δ, ppm: 160.4; 134.9; 133.2; 129.1; 127.7; 124.2; 102.8; 11.2. Found, %: C 53.20; H 4.42; N 9.58. $C_{13}H_{13}BrN_2O$. Calculated, %: C 53.26; H 4.47; N 9.56.

4-Chloro-*N*-(2,5-dimethyl-1*H*-pyrrol-1-yl)benzamide (3j). IR spectrum, ν, cm^{-1}: 3227 (NH), 2891 (Ar CH), 1605 (C=O), 1556 (CH_3), 747 (CCl). ^{1}H NMR spectrum, δ, ppm: 11.35 (1H, s, NH); 7.89 (2H, s, H Ar); 7.89–7.79 (2H, m, H Ar); 5.71 (2H, s, H pyrrole); 2.03 (6H, s, $2CH_3$). ^{13}C NMR spectrum, δ, ppm: 165.4; 132.2; 131.4; 130.0; 127.4; 126.6; 103.7; 11.4. Found, %: C 62.77; H 5.25; N 11.21. $C_{13}H_{13}ClN_2O$. Calculated, %: C 62.78; H 5.27; N 11.26.

4-Fluoro-*N*-(2,5-dimethyl-1*H*-pyrrol-1-yl)benzamide (3k). IR spectrum, ν, cm^{-1}: 3319 (NH), 2462 (Ar CH), 1615 (C=O), 1528 (CH_3), 1177 (CF). ^{1}H NMR spectrum,

δ, ppm (*J*, Hz): 11.11 (1H, s, NH); 8.02 (2H, d, *J* = 7.5, H Ar); 7.31 (2H, d, *J* = 7.5, H Ar); 5.25 (2H, s, H pyrrole); 2.10 (6H, s, $2CH_3$). ^{13}C NMR spectrum, δ, ppm: 168.9; 161.5; 134.0; 131.4; 128.7; 112.6; 103.7; 11.3. Found: C 67.21; H 5.70; N 12.03. $C_{13}H_{13}FN_2O$. Calculated, %: C 67.23; H 5.64; N 12.06.

***N*-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-4-methylbenzamide (3l)**. IR spectrum, ν, cm^{-1}: 3014 (NH), 2781 (Ar CH), 1623 (C=O), 1552 (CH_3). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.32 (1H, s, NH); 7.85 (2H, d, *J* = 7.6, H Ar); 7.32 (2H, d, *J* = 7.5, H Ar); 5.72 (2H, s, H pyrrole); 2.00 (6H, s, $2CH_3$); 1.24 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 168.5; 140.7; 136.0; 132.6; 129.4; 128.4; 103.4; 21.2; 11.1. Found, %: C 73.61; H 7.10; N 12.24. $C_{14}H_{16}N_2O$. Calculated, %: C 73.66; H 7.06; N 12.27.

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The Supplementary material is available for authorized users.

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