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An improved synthesis of pyrimidine- and pyrazole-based acyclo-C-nucleosides as carbohybrids

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ABSTRACT

The synthesis of pyrimidine- and pyrazole-based acyclo-C-nucleosides as carbohybrids was optimized and developed. The synthesis of acyclic polyol-fused pyrimidines was achieved in good to excellent yield with high purity by the cyclocondensation of 2-*C*-formyl glycals and various amidines using K_2CO_3 as inorganic base in co-solvent system. In comparison, the syntheses of pyrazole-based acyclo-C-nucleosides were accomplished simply by the cyclocondensation of 2-*C*-formyl glycals with hydrazine hydrate at room temperature and with phenyl hydrazine at refluxing temperature in ethanol.

The development of practical and efficient route for the synthesis of drug-like small molecules is of considerable interest to medicinal chemists and chemical biologists.[1] Pyrimidines and pyrazoles have been recognized as important heterocyclic compounds due to their frequent use in bioactive natural products and in various pharmaceutical agents.[2,3] The molecules with a pyrimidine core structure exhibit diverse biological activities such as Tie-2 kinase inhibitor,[2b] HIV-1 inhibitor,[2c] antimalarial,[2d] secretive adenosine A1 receptor antagonist,[2e] antibacterial,[2f] and anticancer activities.[2h] Pyrazole derivatives are also known as modulators in biology; for example, they possess anti-obesity,[3a] anti-inflammatory,[3c] estrogen receptor agonist,[3d,e] HIV-1 reverse transcriptase inhibitor,[3f] and anti-hyperglymic activities.[3g] Some bioactive small molecules with pyrimidine or pyrazole substructure are currently used as therapeutic agents (Fig. 1). Therefore, continuous efforts are being made to develop a more efficient and generally applicable synthetic protocol for the synthesis of diversified pyrimidine and pyrazole derivatives.

Peseke and co-workers utilized 'push–pull activation' ability of 2-*C*-formyl glycals and synthesized various molecules in the form of acyclo-C-nucleoside containing pyridine/pyridone[4a,b] and pyrazoles.[4c,d] Peseke also reported three examples of the synthesis of pyrimidine-based acyclo-C-nucleoside from 2-*C*-formyl galactal in poor yield (24–32%); his approach, however, requires the use of strong organic bases (NaOMe) and the reaction time is long (15–20 h).[5] Similarly, Yadav and coworkers reported the synthesis of various pyrazoles from 2-*C*-formyl glucal under microwave conditions and conventional thermal condition.[6]

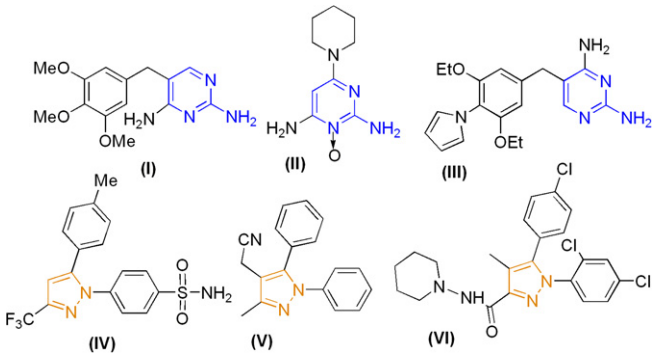

Figure 1. Bioactive small molecules with pyrimidine- and pyrazole-based core skeleton (**I**–**VI**). (**I**) Trimethoprim, antibacterial drug in combination with Sulfamethoxazole; (**II**) Minoxidil, peripheral vasodilator; (**III**) Epiroprim, antibacterial; (**IV**) Celebrex, anti-inflammatory drug; (**V**) PNU-32945, non-nucleoside reverse transcriptase inhibitors; **(VI)** Rimonabant, CB1 receptor inverse agonist.

In continuation of our research on diversity-oriented synthesis (DOS) of drug-like small molecules,[7] we investigated the incorporation of pyrimidine or pyrazole into novel core skeletons since pyrimidine and pyrazole possess interesting biological activities.[7a] Our research campaign came to fruition through our recently reported efficient synthesis of acyclic polyols fused with pyrazolo[1,5-*a*]pyrimidines and 1,2,4-triazolo[1,5-*a*]pyrimidines.[8] In

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addition, we identified that pyrimidine- and pyrazole-based acyclo-C-nucleosides can serve as key intermediates in the formation of various novel core skeletons through further modifications. However, the synthetic protocols reported by Peseke[4c,d,5] cannot satisfy the demands of efficient synthesis of these key intermediates. To satisfy this unmet demand, we systematically monitored the reaction patterns to optimize the reaction conditions in order to improve reaction yield and to shorten the reaction time. In this Letter, we provide a detailed description of reaction optimization for the synthesis of pyrimidine- and pyrazole-based acyclo-C-nucleosides as carbohybrids.

The synthetic protocol was as follows: 2-*C*-formyl glucal **1** was obtained from 3,4,6-tri-*O*-benzyl glucal via the Vilsmeier-Haack reaction.[9] Initially, we attempted to synthesize pyrimidine derivatives by the condensation of 2-*C*-formyl glucal **1** and guanidinium salt **3** in the presence of NaOMe in methanol, based on the previously reported procedure;[5] however, we obtained the desired pyrimidine **10** in very poor yield along with unidentifiable polar byproducts. From the reaction mechanism of push–pull activation, it is apparent that an appropriate base is necessary to activate the dinucleophiles in order to perform the cyclocondensation reaction for the formation of pyrimidines. Therefore, we screened other organic bases (NaH and *t*-BuOK) instead of NaOMe to determine their suitability as agents that can bring about this transformation; however, all these bases failed to improve the reaction yields or shorten the completion time. In all studied cases, we obtained very poor yields (20%) along with some polar mass formed at the bottom of TLC, which led us to believe that the poor yield of pyrimidine **10** might be due to the instability of 2-*C*-formyl glucal **1** against strong organic bases in a polar solvent under the conventional thermal condition.

In order to test our hypothesis, we tested this reaction by using the above-mentioned bases—NaH and *t*-BuOK—in a co-solvent system, that is, ethanol/THF (1:1); however, we only observed a similar or slightly higher yield in all the cases without any significant improvements. We also screened various bases for the appropriate activation of guanidine **3** in a salt-free form without any destabilization of our substrate **1**. As shown in entry 1 of Table 1, this transformation can be completed within 12 h at 80 °C by using K_2CO_3 as the base in a co-solvent system of ethanol/THF (1:1) in an improved yield (45%). As shown in entry 2 of Table 1, the desired pyrimidine **10** was obtained in acceptable yield (60%) after stirring for 17 h through the cyclocondensation of 2-*C*-formyl glucal **1** with guanidinium salt **3** using *n*-BuLi as the base in THF at temperature ranging from 0 °C to room temperature.

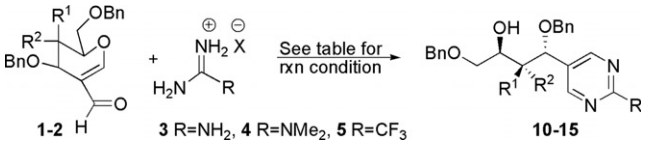
At this juncture, we expanded the scope of dinucleophiles to demonstrate the generality of this transformation. In the case of cyclocondensation of 2-*C*-formyl glucal **1** with 1,1′-dimethylguanidinium salt **4**, we observed further improvements in the yields of desired pyrimidine **11** (Table 1, entries 4 and 5) at room temperature only when compared to the guanidinium salt case (Table 1, entries 1 and 2); this improvement can be explained on the basis of relative nucleophilicity, that is, 1,1′-dimethylguanidine is more nucleophilic than unsubstituted guanidine. In comparison, the same transformation with trifluoroacetamidine **5**, which is less nucleophilic than guanidine, without any base under conventional thermal condition in refluxing ethanol was not very clean and gave only 25% isolable yield of desired pyrimidine **12** (data not shown) even after 12 h. However, by microwave irradiation of 2-*C*-formyl glucal **1** at 90 °C with trifluoroacetamidine **5** under neat condition, the intrinsically lower nucleophilicity of dinucleophiles could be overcome, and we were able to obtain the pyrimidine derivative **12** in good yield (70%) within 10 min (Table 1, entry 6). This was only possible because trifluoroacetamidine **5** was supplied as an acid-free liquid. Therefore, the reaction can be carried out under neat conditions and microwave irradiation in the absence of a base.

With the available optimized conditions, we investigated the scope of the cyclocondensation of 2-*C*-formyl galactal[9] **2** with guanidinium salt **3**, 1,1′-dimethyl guanidinium salt **4** and trifluoroacetamidine **5**. As shown in entries 7–9 of Table 1, 2-*C*-formyl galactal **2** was successfully coupled with all three nucleophiles **3**–**5** under optimized reaction conditions, and the respective pyrimidines **13**–**15** were obtained in excellent yields (72–87%). It is worth mentioning that compound **13** was obtained in 32% yield using the reported procedure,[5] whereas our optimized reaction condition can provide compound **13** in 86% isolable yield (Table 1, entry 7).

After the synthesis of acyclic polyol-fused pyrimidines using guanidinium salt, we further expanded the scope of this transformation with respect to both 2-*C*-formyl glycals (**1**–**2**) and benzamidines (**6**–**7**) to synthesize pyrimidine-based hetero-biaryl compounds.[10] Benzamidines (**6**–**7**) in the salt form were initially treated with 2-*C*-formyl glucal **1** in the presence of K_2CO_3 in a co-solvent system (EtOH/THF, 1:1) at room temperature; in this reaction, no desired products were identified (Table 2, entries 1 and 3). In comparison, 2-*C*-formyl glucal **1** was successfully coupled with benzamidines (**6**–**7**) under the reflux condition, and the respective pyrimidine-based hetero-biaryl compounds **16** and **17** were produced in excellent yields (Table 2, entries 2 and 4). Based on this efficient transformation, the molecular diversity on these hetero-biaryl skeletons could be introduced simply by using differently substituted benzamidines under identical reaction conditions.

Under microwave irradiation, 2-*C*-formyl glucal **1** was successfully condensed with the salt-free form of benzamidines **6**–**7** in the neat condition at 110 °C and the desired hetero-biaryl compounds

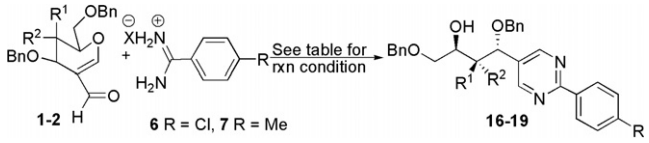
Table 1
Reaction optimization for the synthesis of pyrimidine derivatives



1-2 **3** R=NH_2, **4** R=NMe_2, **5** R=CF_3 **10-15**

Entry	Substrate	Amidines	Reaction condition	R	R^1	R^2	Product	Yield (%)
1	**1**	**3**	EtOH/THF (1:1), K_2CO_3, 80 °C, 12 h	NH_2	H	OBn	**10**	45
2	**1**	**3**	THF, *n*-BuLi, 0 °C to rt, 17 h	NH_2	H	OBn	**10**	60
3	**1**	**4**	MeOH, K_2CO_3, rt, 6 h	NMe_2	H	OBn	**11**	46
4	**1**	**4**	EtOH/THF (1:1), K_2CO_3, rt, 7 h	NMe_2	H	OBn	**11**	59
5	**1**	**4**	THF, *n*-BuLi, 0 °C to rt, 19 h	NMe_2	H	OBn	**11**	65
6	**1**	**5**	μW, 200 W, 90 °C, 10 min	CF_3	H	OBn	**12**	70
7	**2**	**3**	EtOH/THF (1:1), K_2CO_3, 80 °C, 12 h	NH_2	OBn	H	**13**	86
8	**2**	**4**	EtOH/THF (1:1), K_2CO_3, rt, 10 h	NMe_2	OBn	H	**14**	87
9	**2**	**5**	μW, 200 W, 90 °C, 10 min	CF_3	OBn	H	**15**	72

Table 2
Improved synthesis of pyrimidine-based hetero-biaryls



Entry	Substrate	Benzamidines[a]	Reaction condition	R	R^1	R^2	Product	Yield (%)
1	**1**	**6**	EtOH/THF (1:1), K_2CO_3, rt, 4 h	Cl	H	OBn	NR	—
2	**1**	**6**	EtOH/THF (1:1), K_2CO_3, 80 °C, 2 h	Cl	H	OBn	**16**	85
3	**1**	**7**	EtOH/THF (1:1), K_2CO_3, rt, 4 h	Me	H	OBn	NR	—
4	**1**	**7**	EtOH/THF (1:1), K_2CO_3, 80 °C, 12 h	Me	H	OBn	**17**	80
5[b]	**1**	**6**	μW, 200 W, 110 °C, 10 min	Cl	H	OBn	**16**	79
6[b]	**1**	**7**	μW, 200 W, 110 °C, 10 min	Me	H	OBn	**17**	77
7	**2**	**6**	EtOH/THF (1:1), K_2CO_3, 80 °C, 2 h	Cl	OBn	H	**18**	87
8	**2**	**7**	EtOH/THF (1:1), K_2CO_3, 80 °C, 11 h	Me	OBn	H	**19**	82

[a] HI salt of **6** and HCl salt of **7** is used.
[b] Salt-free forms of benzamidines were used in this case. NR = no reaction.

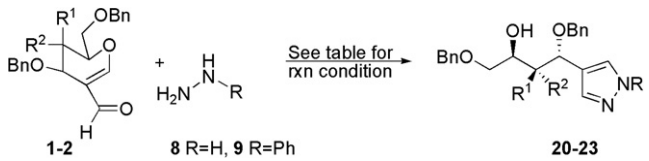
16–**17** were obtained in good yield (77–79%) within 10 min (Table 2, entries 5 and 6). The key feature of this transformation is that benzamidines can be easily activated under microwave irradiation and neat conditions. Using optimized reaction condition, 2-*C*-formyl galactal **2** was also cyclocondensed with benzamidines **6**–**7**, and the respective hetero-biaryl derivatives **18**–**19** were obtained in excellent yields (Table 2, entries 7 and 8). On the basis of the reported procedure, the hetero-biaryl-type compound **19** can only be obtained in 28% yield after 20 h of reaction,[5] whereas our optimized procedure can significantly improve the yield (82%) with a shorter reaction time (Table 2, entry 8).

For the synthesis of acyclic polyol-fused pyrazole derivatives, 2-*C*-formyl glycals (**1**–**2**) were subjected to cyclocondensation with hydrazines (**8**–**9**).[6] To our pleasant surprise, the desired pyrazole derivative **20** was obtained in excellent yield (83%) at room temperature after stirring 2-*C*-formyl glucal **1** and hydrazine hydrate **8** in ethanol for only 2 h (Table 3, entry 1). When the same transformation of 2-*C*-formyl glucal **1** was tried with phenylhydrazine **9** at room temperature, no desired product was observed (Table 3, entry 2), whereas under the conventional thermal conditions as well as microwave irradiation, the desired product **21** was obtained in excellent yield (Table 3, entries 3 and 4). Similarly, 2-*C*-formyl galactal **2** was successfully condensed with hydrazine **8** at room temperature and with phenylhydrazine **9** under the reflux condition, which yielded the desired pyrazole derivatives **22** and **23**, respectively, in excellent yields (Table 3, entries 5 and 6). When 2-*C*-formyl galactal **2** was reacted with phenyl hydrazine **9** using microwave irradiation at 80 °C for 6 min, pyrazole derivative **23** was obtained in 82% isolable yield (Table 3, entry 7).

In summary, we have optimized and developed an improved, practical, and environmentally friendly protocol for the synthesis of pyrimidine- and pyrazole-based acyclo-C-nucleoside through the cyclocondensation of 2-*C*-formyl glucal **1** and 2-*C*-formyl galactal **2** into pyrimidines (**10**–**15**), pyrimidine-based hetero-biaryls (**16**–**19**), and pyrazoles (**20**–**23**) in good to excellent yields. By adopting our improved synthetic protocol, the desired pyrimidine and pyrazole intermediates can be synthesized on a grams scale without any risk of hazards, along with all possible combination of skeletal, building block, and stereochemical diversity elements. We successfully demonstrated this transformation with respect to both 2-*C*-formyl glycals **1**–**2** and various dinucleophiles **3**–**9**, which were all successfully transformed into their respective desired products under the optimized reaction condition. Further modifications and diversifications as well as the associated biological evaluations will be reported in due course.

General experimental procedure: (see Supplementary data for detailed experimental procedure) *Preparation of compounds* **10** *and* **16** *using* K_2CO_3 *in EtOH/THF (1:1)*: To a stirred suspension of K_2CO_3 (172.5 mg, 1.25 mmol, 5.0 equiv) and respective guanidinium salt **3** (2.0 equiv) in EtOH (2.0 mL), 2-*C*-formyl glucal **1** (110 mg, 0.250 mmol) in THF (2.0 mL) was added and resulting mixture was heated at 80 °C until disappearance (TLC) of 2-*C*-formyl glucal **1** (12 h). The resulting reaction mixture was concentrated in vacuum and subjected to flash column chromatography purification to obtain the respective pure product **10** in 45% isolable yield. A similar reaction condition was applied for the synthesis of compound **16** using benzamidine salt **6**. *Compound* **10**: Amorphous solid, $[\alpha]_D^{28}$ −42.74 (*c* 0.340, CH_2Cl_2); TLC: R_f = 0.20 (7:3, EtOAc/

Table 3
Improved synthesis of pyrazole derivatives



Entry	Substrate	Hydrazines	Reaction condition	R	R^1	R^2	Product	Yield (%)
1	**1**	**8**	EtOH, rt, 2 h	H	H	OBn	**20**	83
2	**1**	**9**	EtOH, rt, 8 h	Ph	H	OBn	NR	—
3	**1**	**9**	EtOH, 80 °C, 10 h	Ph	H	OBn	**21**	77
4	**1**	**9**	μW, 250 W, 80 °C, 6 min	Ph	H	OBn	**21**	80
5	**2**	**8**	EtOH, rt, 2 h	H	OBn	H	**22**	95
6	**2**	**9**	EtOH, 80 °C, 10 h	Ph	OBn	H	**23**	79
7	**2**	**9**	μW, 250 W, 80 °C, 6 min	Ph	OBn	H	**23**	82

hexane, v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (s, 2H), 7.34–7.10 (m, 15H), 5.14 (br s, 2H, NH_2), 4.56 (d, J = 3.0 Hz, 1H), 4.53 (d, J = 12.0 Hz, 1H), 4.50 (br s, 2H), 4.39 (d, J = 11.0 Hz, 1H), 4.26 (d, J = 11.0 Hz, 1H), 4.25 (d, J = 12.0 Hz, 1H), 4.00 (m, 1H), 3.60 (m, 2H), 3.55 (dd, J = 7.0 Hz and J = 3.5 Hz, 1H), 2.75 (d, J = 6.0 Hz 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0, 158.4, 137.9, 137.5, 137.4, 128.8, 128.7, 128.6, 128.5, 128.2, 128.1, 121.5 81.6, 76.5, 74.7, 73.7, 71.3, 71.1, 70.2; FAB-HRMS m/z calcd for $C_{29}H_{31}N_3O_4$ $[M+H]^+$: 486.2393; found: 486.2396. *Compound* **16**: Sticky Oil, $[\alpha]_D^{28}$ −48.47 (c 0.346, $CHCl_3$); TLC: R_f = 0.49 (2:3, EtOAc/hexane, v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (s, 2H), 8.39 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 7.33–7.25 (m, 10H), 7.16–7.15 (m, 3H), 7.00 (dd, J = 7.0 Hz and 2.5 Hz, 2H), 4.76 (d, J = 2.5 Hz, 1H), 4.58 (d, J = 12.0 Hz, 1H), 4.52 (br s, 2H), 4.37 (d, J = 11.5 Hz, 1H), 4.32 (d, J = 11.5 Hz, 1H), 4.14 (d, J = 11.5 Hz, 1H), 4.04 (m, 1H), 3.64 (br d, J = 4.0 Hz, 2H), 3.61 (dd, J = 7.5 Hz and 2.5 Hz, 1H), 2.57 (d, J = 4.5 Hz 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 157.0, 137.8, 137.2, 137.1, 137.0, 136.1, 130.1, 129.7, 129.1, 128.8, 128.7, 128.6, 128.5, 128.3, 81.2, 76.5, 74.6, 73.8, 72.0, 70.8, 70.1; LRMS m/z calcd for $C_{35}H_{33}ClN_2O_4$ $[M+H]^+$: 581.22; found: 581.25.

Acknowledgments

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Supplementary data

General experimental and synthetic procedures, complete spectral data and the copies of ^{1}H and ^{13}C NMR spectra of all compounds **10**–**23** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.06.032.

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