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Solvent-free multicomponent synthesis of pyranopyrazoles: per-6-amino-β-cyclodextrin as a remarkable catalyst and host

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ABSTRACT

A simple, green and efficient protocol is developed with per-6-amino-β-cyclodextrin (per-6-ABCD) which acts simultaneously as a supramolecular host and as an efficient solid base catalyst for the solvent-free syntheses of various dihydropyrano[2,3-*c*]pyrazole derivatives involving a four-component reaction. This atom-economical protocol, reported for the first time with ketones also, includes a much milder procedure, does not involve any tedious work-up or purification, avoids hazardous reagents/byproducts and results in near quantitative yields. The catalyst can be reused at least six times without any change in its catalytic activity.

1. Introduction

Organic syntheses oriented towards 'Green Chemistry' evoke increasing interest in recent years[1] resulting in new environmentally benign procedures such as solvent-free syntheses, multicomponent reactions and reusable heterogeneous catalysts to save resources and energy. These organic reactions possess advantages over traditional reactions in organic solvents. For example, solvent-free, multicomponent reactions with reusable heterogeneous catalysts reduce the consumption of environmentally unfriendly solvents and utilize scaled-down reaction vessels. Recently, several techniques for the efficient use of solvent-free reactions,[2] reusable heterogeneous catalyzed reactions[3] and multicomponent reactions[3a,4] have been developed individually but when these three wings of green chemistry can be combined, an excellent green chemistry protocol is expected.[5]

One of the main challenges in medicinal chemistry is the design and synthesis of biologically active molecules.[6] Dihydropyrano[2,3-*c*]pyrazoles play an essential role as biologically active compounds and represent an interesting template for medicinal chemistry. Many of these compounds are known for their antimicrobial,[7] insecticidal[8] and anti-inflammatory activities.[9] Furthermore dihydropyrano[2,3-*c*]pyrazoles show molluscicidal activity[10,11] and are identified as a screening kit for Chk1 kinase inhibitor.[12] They also find applications as pharmaceutical ingredients and biodegradable agrochemicals.[13–15]

During the last few years, synthesis of dihydropyrano[2,3-*c*]pyrazoles has received great interest.[15–27] Otto[16] has used a reaction sequence involving base-catalyzed cyclization of 4-aryliden-5-pyrazolone. Pyranopyrazole is also synthesized from the reaction between 3-methyl-1-phenylpyrazolin-5-one and tetracyano ethylene.[13] In addition, weak bases can also be used for this Michael-type cyclization.[17,18] A three-component condensation[19] between *N*-methylpiperidone, pyrazolin-5-one and malononitrile in absolute ethanol and a two-component reaction[20] involving pyran derivatives and hydrazine hydrate to obtain pyranopyrazoles are also reported. Other recent methods for the synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazoles include synthesis in aqueous media,[21,22] use of piperidine as a base in water,[23] *N*-methylmorpholine in ethanol,[24] microwave irradiation[25] and also solvent-free conditions.[26,27a,b] Herein, we report a facile, general and efficient method to prepare 1,4-dihydropyrano[2,3-*c*]pyrazoles.

Cyclodextrins (CDs), obtained from enzymatic degradation of starch are cyclic oligosaccharides which catalyze a wide range of chemical and photochemical reactions through the formation of a reversible host–guest complex via non-covalent interactions.[28,29] Modification of CDs improves their properties and enhances their capability for complexation with guest molecules resulting in significant increase in their applications in catalysis.[30] Amino-CDs are homogeneous CD derivatives modified by persubstitution at the primary face with amino pendant groups and this manifests combined hydrophobic and electrostatic binding of guest molecules relative to native CDs. They are also employed as biomimetic catalysts in Kemp elimination,[30a] deprotonation[30b] and chiral recognition processes.[30c] In our group, per-6-amino-β-cyclodextrin (per-6-ABCD) is used extensively as a supramolecular chiral host

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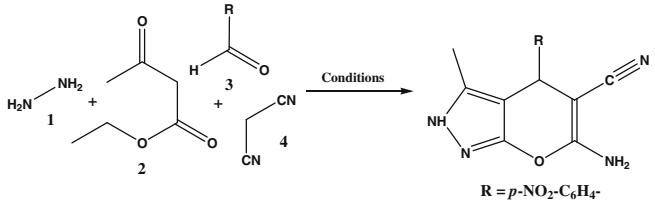
Table 1
Optimization of reaction conditions[a] for the synthesis of pyranopyrazole from 4-nitrobenzaldehyde



Entry	Catalyst	Medium	Time (h)	Yield (%)
1	β-CD	Water	24	Nil
2	Triethylamine	—	10	40.5
3	Diethylamine	—	10	56.2
4	Methylamine[b]	—	10	61.2
5	Piperidine	—	10	68.1
6	Per-6-ABCD	DMF	24	58.2
7	Per-6-ABCD	DMSO	24	61.6
8	Per-6-ABCD	—	1 min	>99
9	Per-6-ABCD	—	1 min	>99[c]
10	Per-6-ABCD	—	1 min	98.0[d]
11	Mono-6-ABCD	—	1 min	51.0

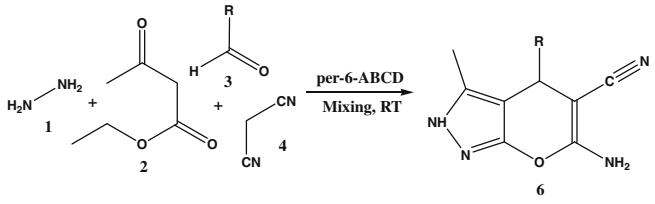
[a] Reactions were performed on a 1 mmol scale of all reactants in solvent-free conditions at room temperature.
[b] 40% solution of methylamine in water.
[c] 0.008 mmol per-6-ABCD as catalyst.
[d] 0.0001 mmol per-6-ABCD as catalyst.

and as a base catalyst for Cu-catalyzed N-arylation[31] and for Michael addition of nitromethane to chalcones.[32] In the present work, we have utilized per-6-ABCD as an excellent supramolecular host for the synthesis of pyranopyrazole derivatives,[33] in an efficient and ecofriendly four-component reaction protocol under solvent-free conditions at room temperature. It is also interesting to note that the catalyst can be recovered and reused several times.

2. Results and discussion

Hydrazine hydrate, ethyl acetoacetate, 4-nitrobenzaldehyde and malononitrile are taken as model substrates to optimize reaction conditions and the results are discussed in Table 1. When β-CD is used as a catalyst in aqueous medium, at room temperature, there is no reaction (entry 1). The reaction is also studied using conventional bases such as triethylamine (entry 2), diethylamine (entry 3), methylamine (entry 4) and piperidine (entry 5) as a catalyst in solvent-free conditions (entries 2–5). In all cases the yield of the product is limited and also its separation from the reaction mixture is difficult. When per-6-ABCD is used as a catalyst for this reaction in DMF and DMSO, similar yields are obtained (entries 6 and 7). However, to our surprise, when the catalyst is mixed with the reactants under solvent-free conditions, 100% yield is obtained (entry 8) within one minute. Even with catalytic amount of per-6-ABCD (0.008 mmol), successive addition of hydrazine hydrate, ethyl acetoacetate, aldehyde/ketone and malononitrile has re-

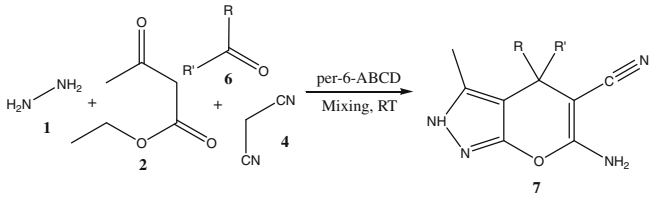
Table 2
Synthesis of pyranopyrazoles[33] with various substituted aldehydes[a]



Entry	R in aldehyde	Yield (%)	Entry	R in aldehyde	Yield (%)
1	C_6H_5–	>99	14	*p*-OCH_3–C_6H_4–	99
2	1-Pyrenyl–	>99	15	*m*-OCH_3–C_6H_4–	>99
3	*p*-NO_2–C_6H_4–	>99	16	*p*-CH_3–C_6H_4–	>99
4	*m*-NO_2–C_6H_4–	>99	17	*p-i-Pr*-C_6H_4–	>99
5	*p*-Cl–C_6H_4–	>99	18	C_6H_5–CH=CH–	98
6	*m*-Cl–C_6H_4–	99	19	CH_3–CH=CH–	97
7	*o*-Cl–C_6H_4–	99	20	*m*-CH_3–C_6H_4–	99
8	*m, p*-Cl_2–C_6H_3–	>99	21	2′-Furanyl–	>99
9	*p*-F–C_6H_4–	>99	22	2′-Thiophenyl–	>99
10	*p*-Br–C_6H_4–	>99	23	4′-Pyridinyl–	>99
11	*p*-OH–C_6H_4–	>99	24	Cyclohexyl–	>99
12	*o*-OH–C_6H_4–	99	25	CH_3–	60
13	*p*-NMe_2–C_6H_4–	>99	26	H–	Trace

[a] Reactions were performed on a 1 mmol scale of all reactants with 0.008 mmol per-6-ABCD in solvent-free conditions for 1 min at room temperature.

Table 3
Synthesis of pyranopyrazoles[33] with various substituted ketones[a]



Entry	Ketone		Yield (%)
	R	R′	
1	C_6H_5–	CH_3–	>99
2	C_6H_5–	CH_3–CH_2–CH_2–	99
3	*p*-Br–C_6H_4–	CH_3–	>99
4	*p*-Cl–C_6H_4–	CH_3–	>99
5	*o*-Cl–C_6H_4–	CH_3–	>99
6	*p*-NH_2–C_6H_4–	CH_3–	>99
7	*o*-NH_2–C_6H_4–	CH_3–	>99
8	*p*-OH–C_6H_4–	CH_3–	>99
9	*o*-OH–C_6H_4–	CH_3–	99
10	*p*-OCH_3–C_6H_4–	CH_3–	>99
11	*p*-CH_3–C_6H_4–	CH_3–	99
12	2′-Naphthyl–	CH_3–	>99
13	1′-Naphthyl–	CH_3–	99
14	5-Bromothiophene–	CH_3–	>99
15	5-Chlorothiophene–	CH_3–	>99
16	1-Piperazine–	CH_3–	98
17	2-Pyrrole–	CH_3–	>99
18	4-Pyridine–	CH_3–	>99
19	C_6H_5–	C_6H_5–	99
20	*p*-Cl–C_6H_4–	C_6H_5–	>99
21	*p*-NH_2–C_6H_4–	C_6H_5–	>99
22	*o*-NH_2–C_6H_4–	C_6H_5–	>99
23	*p*-OCH_3–C_6H_4–	C_6H_5–	99
24	*p*-CH_3–C_6H_4–	C_6H_5–	98
25	*p*-Br–C_6H_4–	C_6H_5–CH=CH–	96
26	*p*-OCH_3–C_6H_4–	C_6H_5–CH=CH–	94
27	CH_3–	$(OCH_3)_2$CH–CH_2–	62

[a] Reactions were performed on a 1 mmol scale of all reactants with 0.008 mmol per-6-ABCD in solvent-free conditions for 1 min at room temperature.

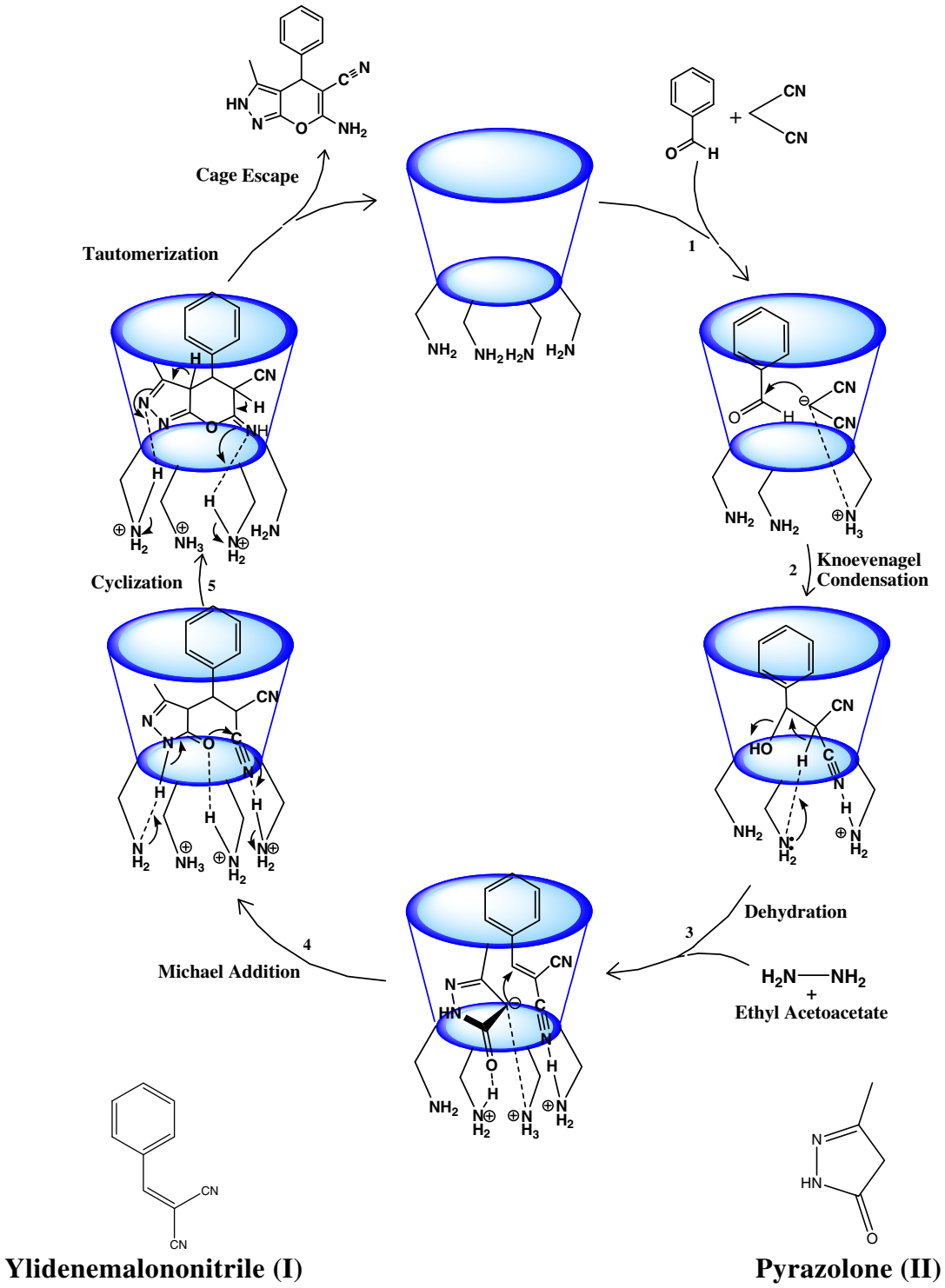
Table 4
Reusability of per-6-ABCD as a catalyst in the synthesis of pyranopyrazoles from *p*-NO_2–C_6H_5–CHO[a]

Run[b]	First	Second	Third	Fourth	Fifth	Sixth
Yield (%)	100	100	100	99.9	99.8	99.7

[a] Reactions were performed on a 1 mmol scale of all reactants in solvent-free conditions for 1 min at room temperature.
[b] After completion of the reaction, 1 ml of ethanol was added to the reaction mixture and the precipitated per-6-ABCD was removed by filtration, washed with distilled ethanol (1 ml) for three times, dried in vacuum and reused. The products were obtained by evaporating the combined ethanol portions.

sulted in quantitative yield of pyranopyrazoles under solvent-free conditions (entry 9). Even here the reaction is very fast and gets completed within 1 min. The result is similar even with 0.0001 mmol of catalyst (entry 10). The product is obtained not only in excellent yield (100%) but also in excellent purity. Atom economy is also very good in this reaction with only ethanol as the side product. As the product is pure, there is no need for further purification. When mono-6-amino-β-CD, prepared as per reported procedure,[35] is used as the catalyst, the reaction proceeds with reduced yield and this highlights a more significant role for per-6-ABCD catalyst. This study thus demonstrates the efficiency of per-6-ABCD as an excellent supramolecular host as well as a reusable base catalyst with high turnover number.

This easy and clean protocol for the synthesis of functionalized pyranopyrazoles is extended to various substituted aldehydes and ketones and the observed results are presented in Tables 2 and 3. The catalyst is also found to be reusable (Table 4). After completion of the reaction, per-6-ABCD is filtered, washed with ethanol for



Scheme 1. Proposed mechanism for per-6-ABCD-catalyzed synthesis of pyranopyrazoles.

three times, dried in vacuum and reused. Upto six runs, there is no change in the catalytic efficiency.

Perusal of literature[23] shows that a tandem sequence of base-catalyzed reactions is proposed to account for the formation of pyranopyrazoles. The first step involves formation of pyrazolone by the reaction between hydrazine and ethyl acetoacetate. In the second step, ylidenemalononitrile is formed by Knoevenagel condensation between malononitrile and aldehyde. In the third step, Michael addition of pyrazolone to ylidenemalononitrile takes place followed by cyclization and tautomerization to give the pyranopyrazoles.

To account for the very efficient catalysis by per-6-ABCD, of this tandem reaction, wherein base-catalyzed reactions are involved, it is proposed that per-6-ABCD with its seven free primary amino groups acting synergistically behaves as an efficient supramolecular host and base catalyst (Scheme 1). In the first step, the aldehyde/ketone binds to the CD cavity. Abstraction of a proton from malononitrile by per-6-ABCD catalyzes its Knoevenagel condensation with the carbonyl group to give the ylidenemalononitrile (I).

The cooperative enzyme-like binding of these intermediates which ensure their tighter fit into the cavity facilitates further reactions, namely Michael addition of pyrazolone (II) to ylidenemalononitrile (by abstraction of a proton from pyrazolone), cyclization and tautomerization. It is also likely that the formation of ylidenemalononitrile (I) and pyrazolone (II) may take place outside the per-6-ABCD cavity and then they can go into the cyclodextrin cavity. The proposed mechanism is also supported by observations of peaks in UV corresponding to intermediates ylidenemalononitrile (I) and pyrazolone (II) when the reaction is carried out in DMF (see Supplementary data, Fig. S1). Binding constants for intermediates I, II and the product are also evaluated and found to be 1283, 1310 and 984 M^{-1}, respectively. Hydrogen bonding interaction with the secondary hydroxyl groups of per-6-ABCD (Scheme 1) may also contribute to the faster reactivity.

To ensure that the reaction involves inclusion of all the reactants inside the CD cavity which looks essential for the catalytic activity of per-6-ABCD (the enzyme-like cooperative binding of all reactants and their closer proximity to the catalytic amino groups which are suitably oriented and are acting synergistically thus ensuring faster reactivity), the following control experiments are carried out (Table 5). With ethylenediamine (4 equiv, compared to 4-nitrobenzaldehyde) as the base catalyst, the reactants are stirred for 24 h in water in the absence of β-CD (entry 1). The experiment is also carried out in solid phase (entry 2). The above-described experiment is repeated with equimolar amount of β-CD, both in solution and in solid phase (entries 3 and 4). In all the cases, the bisimine of 4-nitrobenzaldehyde with ethylenediamine is obtained as the only product.

Per-6-ABCD is treated with equimolar amount of adamantane, which forms an inclusion complex (binding constant for adamantane/per-6-ABCD inclusion complex is found to be 1824 M^{-1} in the present study). Then the reaction is carried out with this adamantane included per-6-ABCD, in DMF at 24 h (entry 5) and also in solvent-free conditions (entry 6). Control experiments (entries 7 and 8) are also carried out with adamantanol included per-6-ABCD (binding constant 2248 M^{-1}) and also with adamantane/adamantanol included mono-6-ABCD (entries 9–12). Absence of any reaction in all the cases confirms that inclusion into per-6-ABCD cavity is essential for catalytic activity.

Only ~5% to 6% of pyranopyrazole is formed in DMF. In solvent-free conditions, no product formation is observed. In our view, these control experiments strongly suggest that inclusion is essential to promote the reaction. In addition, the enhanced reactivity observed in the present study is also attributed to the synergistic effect of all the seven amino groups present in proximity which ensures enzyme-like reactivity and catalysis.

Table 5
Control experiments[a] in the synthesis of pyranopyrazoles from *p*-NO_2–C_6H_5–CHO

Entry	Catalyst	Medium	Time (h)	Yield (%)
1	Ethylenediamine (1:4)[b]	Water	24	Nil
2	Ethylenediamine (1:4)[b]	—	24	Nil
3	Ethylenediamine + β-CD (1:4)[b]	Water	24	Nil
4	Ethylenediamine + β-CD (1:4)[b]	—	24	Nil
5	Per-6-ABCD + adamantane[c] (1:1)[b]	DMF	24	2.6
6	Per-6-ABCD + adamantane[c] (1:1)[b]	—	24	—
7	Per-6-ABCD + adamantanol[c] (1:1)[b]	DMF	24	—
8	Per-6-ABCD + adamantanol[c] (1:1)[b]	—	24	—
9	Mono-6-ABCD + adamantane[c] (1:1)[b]	DMF	24	5
10	Mono-6-ABCD + adamantane[c] (1:1)[b]	—	24	—
11	Mono-6-ABCD + adamantanol[c] (1:1)[b]	DMF	24	6
12	Mono-6-ABCD + adamantanol[c] (1:1)[b]	—	24	—

[a] Reactions are performed on a 1 mmol scale of all reactants with per-6-ABCD in solvent/solvent-free conditions at room temperature.
[b] Ratio of substrate:catalyst.
[c] 1:1 complex formed by freeze-drying method.

Table 6
Free energy changes in the reactants, intermediates formed during the reaction and the product (both without and inside per-6-ABCD cavity)[a]

Steps in Scheme 1	ΔE (kcal/mol)	
	Without CD	Inside CD cavity[b]
1	24.3431	−24.5743
2	42.7437	−25.0356
3	68.8782	−85.4123
4	47.6696	−80.1566
5	57.5345	−38.3200
Final product	55.2510	−32.2009
Total ΔE	296.4201	−285.6997

[a] Error limit 0.0001 kcal/mol.
[b] ΔE can be calculated from $\Delta E_{Complex} - \Delta E_{Host} - \Delta E_{Guest}$.

The proposed mechanism (Scheme 1) also finds strong support from energy minimization studies. Molecular modelling and energy minimization calculations are performed using Insight II/Discover program in IRIX system. First, the energy change of the reactants and intermediates in the absence and presence of per-6-ABCD is calculated. The energy minimization studies are carried out using different mode of inclusion of substrates in per-6-ABCD cavity (see Supplementary data, Figs. S2–S7).

The data, given in Table 6, indicate that when the reaction takes place without per-6-ABCD, the ΔE increases for the various steps (1–5) proposed in Scheme 1. The ΔE for the overall heat of product formation is 296.4201 kcal/mol. On the other hand, when the reaction takes place inside the per-6-ABCD cavity, very significant decrease in ΔE is noticed for steps 1–5 in Scheme 1. This change in ΔE is even more significant for steps 3 and 4 (which involve multicomponent reactions). After the formation of the final pyranopyrazole, ΔE increases resulting in expulsion of the same from the per-6-ABCD cavity and the reaction cycle goes on. The ΔE for the overall heat of product formation is −285.6997 kcal/mol.

3. Conclusion

To summarize, a simple, faster, clean, green and atom-economical solvent-free protocol with high turnover is established for the one-pot synthesis of pyranopyrazoles in excellent yields and purity (without any tedious work-up or purification). Reaction conditions are very simple for substituted aldehydes and ketones (reported extensively for the first time) also react through this tandem reaction. Ethanol is the only product eliminated during the reaction. Only very small amount of this reusable catalyst is used, which is

removed by filtration of ethanolic solution of product. Catalyst can be reused at least six times without any change in its catalytic activity.

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Supplementary data

Supplementary data (complete experimental procedures are provided, including ^{1}H, ^{13}C and HRMS (ESI) spectra, of all compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.087.

References and notes

1. (a) Dittmer, D. C. *Chem. Ind.* **1997**, 779; (b) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025; (c) Hara, K. In *Organic Synthesis at High Pressures*; Matsumoto, K., Acheson, R. M., Eds.; Wiley: New York, 1991; p 423; (d) Ogo, Y. *Petrotechnology* **1988**, *11*, 307.
2. (a) Wang, G.-W.; Komatsu, K.; Murata, Y.; Shiro, M. *Nature* **1997**, *387*, 583; (b) Varma, R. S.; Kumar, D.; Dahiya, R. *J. Chem. Res. (S)* **1998**, 324; (c) Nozoe, T.; Tanimoto, K.; Takemitsu, T.; Kitamura, T.; Harada, T.; Osawa, T.; Takayasu, O. *Solid State Ionics* **2001**, *141*, 695; (d) Lamartine, R.; Perrin, R. In *Spillover of Adsorbed Species*; Pajonk, G. M., Teichner, S. J., Germain, J. E., Eds.; Elsevier: Amsterdam, 1983; p 251.
3. (a) Tsukinoki, T.; Nagashima, S.; Mitoma, Y.; Tashiro, M. *Green Chem.* **2000**, *2*, 117; (b) Ballini, R.; Bosica, G.; Maggi, R.; Ricciutelli, M.; Righi, P.; Sartori, G.; Sartorio, R. *Green Chem.* **2001**, *3*, 178; (c) Amantini, D.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *Green Chem.* **2001**, *3*, 229.
4. Ugi, I. *Pure Appl. Chem.* **2001**, *73*, 187.
5. Sheldon, R. A. *Green Chem.* **2005**, *7*, 267.
6. Hailes, H. C. *Org. Process Res. Dev.* **2007**, *11*, 114.
7. El-Tamany, E. S.; El-Shahed, F. A.; Mohamed, B. H. *J. Serb. Chem. Soc.* **1999**, *64*, 9.
8. Ismail, Z. H.; Aly, G. M.; El-Degwi, M. S.; Heiba, H. I.; Ghorab, M. M. *Egypt J. Biot.* **2003**, *13*, 73.
9. Zaki, M. E. A.; Soliman, H. A.; Hiekal, O. A.; Rashad, A. E. Z. *Naturforsch., C* **2006**, *61*, 1.
10. Abdelrazek, F. M.; Metz, P.; Metwally, N. H.; El-Mahrouky, S. F. *Arch. Pharm.* **2006**, *339*, 456.
11. Abdelrazek, F. M.; Metz, P.; Kataeva, O.; Jaeger, A.; El-Mahrouky, S. F. *Arch. Pharm.* **2007**, *340*, 543.
12. (a) Foloppe, N.; Fisher, L. M.; Howes, R.; Potter, A.; Robertson, A. G. S.; Surgenor, A. E. *Bioorg. Med. Chem.* **2006**, *14*, 4792; (b) Kimata, A.; Nakagawa, H.; Ohyama, R.; Fukuuchi, T.; Ohta, S.; Suzuki, T.; Miyata, N. *J. Med. Chem.* **2007**, *50*, 5053.
13. (a) Junek, H.; Aigner, H. *Chem. Ber.* **1973**, *106*, 914; (b) Sosnovskikh, V. Y.; Barabanov, M. A.; Usachev, B. I.; Irgashev, R. A.; Moshkin, V. S. *Russ. Chem. Bull., Int. Ed.* **2005**, *54*, 2846; (c) El-Assiery, S. A.; Sayed, G. H.; Fouda, A. *Acta Pharm.* **2004**, *54*, 143; (d) Guard, J. A. M.; Steel, P. J. *ARKIVOC* **2001**, *vii*, 32.
14. (a) Wamhoff, H.; Kroth, E.; Strauch, K. *Synthesis* **1993**, *11*, 1129; (b) Tacconi, G.; Gatti, G.; Desimoni, G.; Messori, V. *J. Prakt. Chem.* **1980**, *322*, 831; (c) Sharanina, L. G.; Marshtupa, V. P.; Sharanin, Y. A. *Khim. Geterosikl. Soedin.* **1980**, *10*, 1420.
15. (a) Sharanin, Y. A.; Sharanina, L. G.; Puzanova, V. V. *Zh. Org. Khim.* **1983**, *19*, 2609; (b) Rodinovskaya, L. A.; Gromova, A. V.; Shestopalov, A. M.; Nesterov, V. N. *Russ. Chem. Bull., Int. Ed.* **2003**, *52*, 2207.
16. Otto, H. H. *Arch. Pharm.* **1974**, *307*, 444.
17. Otto, H. H.; Schmelz, H. *Arch. Pharm.* **1979**, *312*, 478.
18. Klokol, G. V.; Krivokolysko, S. G.; Dyachenko, V. D.; Litvinov, V. P. *Chem. Heterocycl. Compd.* **1999**, *35*, 1183.
19. (a) Shestopalov, A. M.; Emeliyanova, Y. M.; Shestopalov, A. A.; Rodinovskaya, L. A.; Niazimbetova, Z. I.; Evans, D. H. *Tetrahedron* **2003**, *59*, 7491; (b) Shestopalov, A. M.; Emeliyanova, Y. M.; Shestopalov, A. A.; Rodinovskaya, L. A.; Niazimbetova, Z. I.; Evans, D. H. *Org. Lett.* **2002**, *4*, 423.
20. Peng, Y.; Song, G.; Dou, R. *Green Chem.* **2006**, *8*, 573.
21. Shi, D.; Mou, J.; Zhuang, Q.; Niu, L.; Wu, N.; Wang, X. *Synth. Commun.* **2004**, *34*, 4557.
22. Jin, T.-S.; Wang, A.-Q.; Cheng, Z.-L.; Zhang, J.-S.; Li, T.-S. *Synth. Commun.* **2005**, *35*, 137.
23. Vasuki, G.; Kumaravel, K. *Tetrahedron Lett.* **2008**, *49*, 5636.
24. Lehmann, F.; Holm, M.; Laufer, S. *J. Comb. Chem.* **2008**, *10*, 364.
25. (a) Zhou, J.-F.; Tu, S.-J.; Zhu, H.-Q.; Zhi, S.-J. *Synth. Commun.* **2002**, *32*, 3363; (b) Shaker, R. M.; Mahmoud, A. F.; Abdel-Latif, F. F. *J. Chin. Chem. Soc.* **2005**, *52*, 563.
26. Guo, S.-B.; Wang, S.-X.; Li, J.-T. *Synth. Commun.* **2007**, *37*, 2111.
27. (a) Ren, Z.; Cao, W.; Tong, W.; Jin, Z. *Synth. Commun.* **2005**, *35*, 2509; (b) Nagarajan, A. S.; Reddy, B. S. R. *Synlett* **2009**, 2002.
28. (a) Takahashi, K. *Chem. Rev.* **1998**, *98*, 2013; (b) Sakuraba, H.; Maekawa, H. *J. Inclusion Phenom. Macrocycl. Chem.* **2006**, *54*, 41; (c) Bhosale, S. V.; Bhosale, S. V. *Mini-Rev. Org. Chem.* **2007**, *4*, 231; (d) Wenz, G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 803.
29. *Cyclodextrin and their Complexes*; Dodziuk, H., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2006.
30. (a) McCracken, P. G.; Ferguson, C. G.; Vizitiu, D.; Walkinshaw, C. S.; Wang, Y.; Thatcher, G. R. J. *J. Chem. Soc., Perkin Trans. 2* **1999**, 911; (b) Kitae, T.; Nakayama, T.; Kano, K. *J. Chem. Soc., Perkin Trans. 2* **1998**, 207; (c) Riela, S.; D'Anna, F.; Meo, L. P.; Gruttadauria, M.; Giacalone, R.; Noto, R. *Tetrahedron* **2006**, *62*, 4323; (d) Brown, S. E.; Coates, J. H.; Duckworth, P. A.; Lincoln, S. F.; Easton, C. J.; May, B. L. *J. Chem. Soc., Faraday Trans.* **1993**, *89*, 1035.
31. Suresh, P.; Pitchumani, K. *J. Org. Chem.* **2008**, *73*, 9121.
32. Suresh, P.; Pitchumani, K. *Tetrahedron: Asymmetry* **2008**, *19*, 2037.
33. *General procedure for the synthesis of the pyranopyrazoles.*
Hydrazine hydrate (0.1 g, 2 mmol), ethyl acetoacetate (0.26 g, 2 mmol), 4-nitrobenzaldehyde (0.30 g, 2 mmol) and malononitrile (0.13 g, 2 mmol) were added successively to per-6-ABCD[34] (0.01 g, 0.008 mmol). The reaction mixture was ground for 1 min at room temperature. After completion of the reaction, 1 ml of distilled ethanol was added to the reaction mixture. The precipitated per-6-ABCD was removed by filtration, washed with distilled ethanol (1 ml) for three times, dried in vacuum and reused. The products were obtained by evaporating the combined ethanol portions. The products were characterized by ^{1}H, ^{13}C-NMR and mass spectral techniques (see Supplementary data).
34. Ashton, P. R.; Koniger, R.; Stoddart, J. F. *J. Org. Chem.* **1996**, *61*, 903.
35. (a) Petter, R. C.; Salek, J. S.; Sikorski, C. T.; Kumaravel, G.; Lin, F.-T. *J. Am. Chem. Soc.* **1990**, *112*, 3860; (b) Tang, W.; Ng, S.-C. *Nat. Protocols* **2008**, *3*, 691.