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Report

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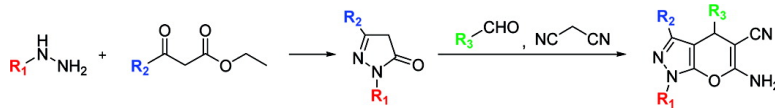

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Three-Component Combinatorial Synthesis of Novel Dihydropyrano[2,3-*c*]pyrazoles

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One of the main challenges in medicinal chemistry is the design and synthesis of biologically active molecules. The discovery of high-throughput screening (HTS) has tremendously increased the need for new testing compounds. In recent decades, the synthesis of combinatorial libraries has been shown to be a useful tool in the search for new lead structures.[1] In this paper, we report the synthesis of a structurally diverse and medicinally interesting series of dihydropyrano[2,3-*c*]pyrazoles via a three-component reaction.

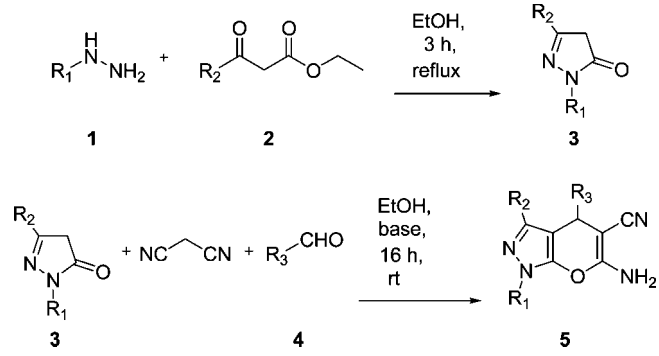
Dihydropyrano[2,3-*c*]pyrazoles play an essential role in biologically active compounds and therefore represent an interesting template for medicinal chemistry. Many of those compounds are known as antimicrobial,[2] insecticidal,[3] and anti-inflammatory.[4] Furthermore dihydropyrano[2,3-*c*]pyrazoles showed molluscicidal activity[5,6] and was identified as a screening hit for Chk1 kinase inhibitor.[7]

Over the last years, the chemistry of dihydropyrano[2,3-*c*]pyrazoles has received great interest. The first approach to synthesize these substances was undertaken by Otto,[8] in which he initiated the reaction sequence by the base-catalyzed cyclization of 4-aryliden-5-pyrazolone. In a further report, this same group showed that weak bases can also be used for a Michael-type cyclization.[9] Extending the work of Otto, Klokol and colleagues performed the direct conversion of 3-methyl-3-pyrazolin-5-one with malononitrile in the presence of a weak base.[10] Recent methods for the synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazoles include synthesis in aqueous media,[11,12] under microwave irradiation,[13] and under solvent-free conditions.[14,15] Herein, we report a general, facile, and efficient method based on the procedure of Klokol et al.[10] to generate wide variety in the substitution pattern of novel 1,4-dihydropyrano[2,3-*c*]pyrazoles.

Our general sequence, outlined in Scheme 1, should allow entrance to 1,4-dihydropyrano[2,3-c]pyrazoles with various substituents at the 1-, 3-, and 4-position. Given the large number of commercially available aldehydes and the easy access to hydrazines and β-keto esters, this method should be applicable to synthesis of libraries with high diversity. We expect this method to find extensive application in the fields of combinatorial chemistry, diversity-oriented synthesis, and drug discovery.

The starting materials for our library synthesis (Scheme 1) were chemsets **1** and **2**. All starting hydrazines (Figure 1) were

Scheme 1. General Sequence for the Preparation of 1,4-Dihydropyrano[2,3-*c*]pyrazoles **5**



purchased or prepared following known procedures.[16,17] The corresponding β-keto esters (Figure 2) were synthesized either according to Yuasa and Tsuruta[18] or by deprotonation of esters and subsequent reaction with ethyl acetate. This second procedure (deprotonation of esters), described in a patent application for the synthesis of ethyl 3-oxo-3-(pyridin-4-yl)propanoate,[19] is more advantageous because the reaction

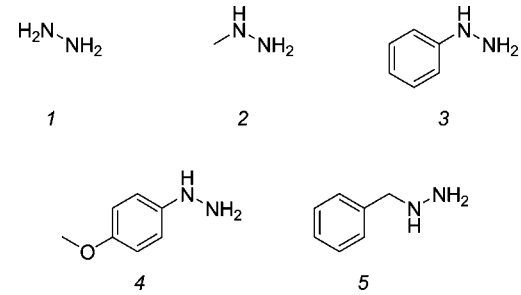


Figure 1. Diversity reagents **1**{*1*−*5*}.

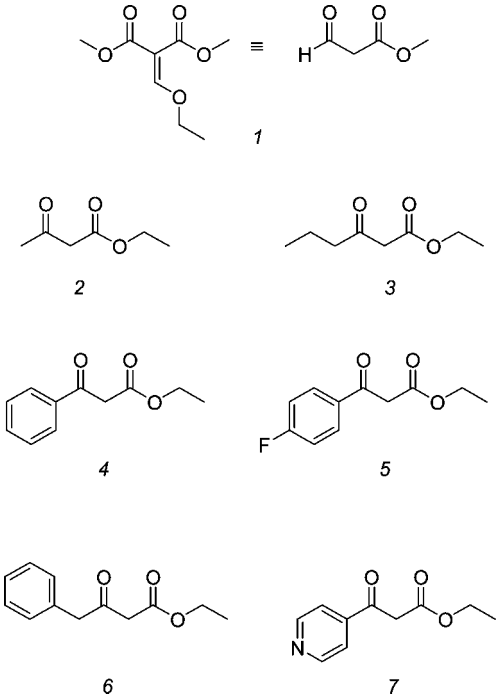


Figure 2. Diversity reagents **2**{*1*−*7*}.

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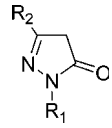
Table 1. Prepared 1*H*-Pyrazol-5(4*H*)-ones, **3**{*1*−*5*,*1*−*7*}, and 1*H*-Pyrazol-5(4*H*)-ones, **3**{*1*−*5*,*1*−*6*}



entry	yield (%)
3{*1*,*2*}	94
3{*2*,*1*}	23
3{*2*,*2*}	99
3{*2*,*5*}	84[a]
3{*3*,*2*}	45
3{*3*,*3*}	99
3{*3*,*4*}	43
3{*3*,*6*}	17
3{*3*,*7*}	99
3{*4*,*2*}	98
3{*4*,*3*}	95
3{*4*,*4*}	38
3{*5*,*2*}	13
3{*5*,*7*}[a]	97

[a] Still unknown substances in literature.

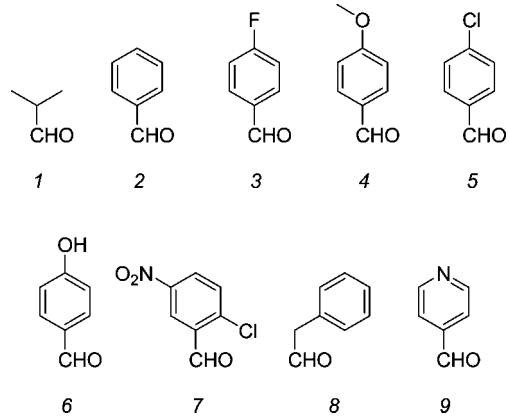


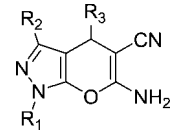
Figure 3. Diversity reagents **4**{*1*−*9*}.

can be performed using ethyl acetate as both the solvent and reagent without further purification. With the method of Yuasa and Tsuruta, the separation of β-keto esters from unreacted ethyl acetoacetate via column chromatography was necessary.

Conversion of chemsets **1** and **2** to **3** (Table 1) was accomplished using the general method described by Butler and DeWald,[20] except for compound **3**{*2*,*1*}, which was obtained by interaction of methylhydrazine with dimethyl-2-(ethoxymethylene)malonate **2**{*1*} (Figure 2), followed by saponification and decarboxylation of the ethyl ester with potassium hydroxide.[21] Compounds **3**{*2*,*5*} and **3**{*5*,*7*} have not been previously reported in the literature.

In a three-component reaction using malononitrile, chemset **3**, and chemset **4** (Figure 3), we prepared the desired dihydropyrano[2,3-*c*]pyrazoles **5**{*1*−*5*;*1*−*7*;*1*−*9*} (Table 2) in a manner analogous to the procedure described for aliphatic aldehydes.[10,22] The ease of preparation of this procedure should be emphasized. The reaction was performed at room temperature overnight, and nearly all products precipitated as discrete crystals. Therefore, no further purification was necessary. The crystals isolated directly from the reaction mixture were pure enough for X-ray analysis.[23] Only two examples have a purity of less than 50% measured

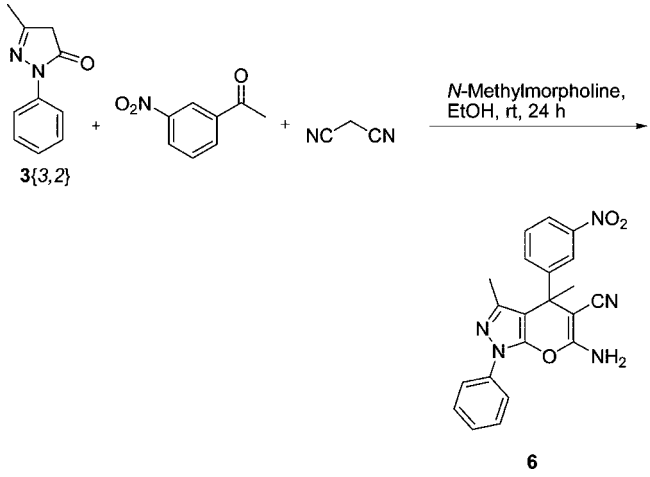
Table 2. Synthesized Dihydropyrano[2,3-*c*]pyrazoles and Derivatives, **5**{*1*−*5*,*1*−*7*,*1*−*9*}, **6**−**9**



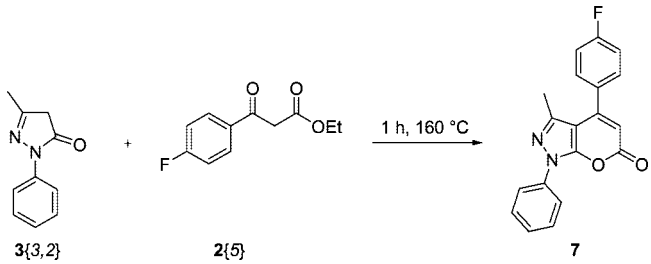
entry	yield (%)	purification
5{*1*,*2*,*2*}[a]	58	cryst
5{*2*,*1*,*4*}	39	cryst
5{*2*,*2*,*1*}	32	CC
5{*2*,*2*,*2*}	73	cryst
5{*2*,*2*,*3*}	39	cryst
5{*2*,*2*,*4*}	35	cryst
5{*2*,*2*,*5*}	44	cryst
5{*2*,*2*,*6*}	87	cryst
5{*2*,*2*,*7*}	90	cryst
5{*2*,*2*,*8*}	14	CC
5{*2*,*5*,*9*}	70	cryst
5{*3*,*2*,*1*}	34	CC
5{*3*,*2*,*2*}[a]	61	cryst.
5{*3*,*2*,*3*}[a]	48	cryst
5{*3*,*2*,*4*}[a]	87	cryst
5{*3*,*2*,*5*}[a]	53	cryst
5{*3*,*2*,*6*}[a]	89	cryst
5{*3*,*2*,*7*}	87	cryst
5{*3*,*2*,*8*}	25	CC
5{*3*,*3*,*1*}	27	cryst
5{*3*,*3*,*2*}	52	cryst
5{*3*,*3*,*3*}	57	cryst
5{*3*,*3*,*4*}	62	cryst
5{*3*,*3*,*5*}	46	cryst
5{*3*,*3*,*6*}	63	cryst
5{*3*,*3*,*7*}	58	cryst
5{*3*,*3*,*8*}	43	CC
5{*3*,*4*,*2*}[a]	36	cryst
5{*3*,*4*,*3*}	38	cryst
5{*3*,*4*,*4*}[a]	62	cryst
5{*3*,*4*,*5*}[a]	47	cryst
5{*3*,*4*,*6*}	47	cryst
5{*3*,*4*,*7*}	55	cryst
5{*3*,*4*,*9*}	58	cryst
5{*4*,*2*,*1*}	14	CC
5{*4*,*2*,*2*}	52	cryst
5{*4*,*2*,*3*}	50	cryst
5{*4*,*2*,*4*}	57	cryst
5{*4*,*2*,*5*}	63	cryst
5{*4*,*2*,*6*}	50	cryst
5{*4*,*2*,*7*}	56	cryst
5{*4*,*2*,*8*}	21	CC
5{*4*,*3*,*2*}	28	cryst
5{*4*,*3*,*3*}	52	cryst
5{*4*,*3*,*4*}	35	cryst
5{*4*,*3*,*5*}	36	cryst
5{*4*,*3*,*6*}	28	cryst
5{*4*,*3*,*7*}	7	cryst
5{*4*,*4*,*2*}	44	cryst
5{*4*,*4*,*3*}	46	cryst
5{*4*,*4*,*4*}	36	cryst
5{*4*,*4*,*5*}	50	cryst
5{*4*,*4*,*6*}	24	cryst
5{*4*,*4*,*7*}	27	cryst
5{*4*,*4*,*8*}	27	CC
5{*5*,*2*,*2*}	5	cryst
5{*5*,*7*,*1*}	30	cryst
5{*5*,*7*,*2*}	34	cryst
5{*5*,*7*,*3*}	30	cryst
5{*5*,*7*,*4*}	38	cryst
5{*5*,*7*,*5*}	31	cryst
5{*5*,*7*,*7*}	31	cryst
6	89	CC
7	34	
8	96	
9	29	

[a] already reported in literature.

Scheme 2. Synthesis of **6** to Exemplify the Use of Ethanone Derivatives



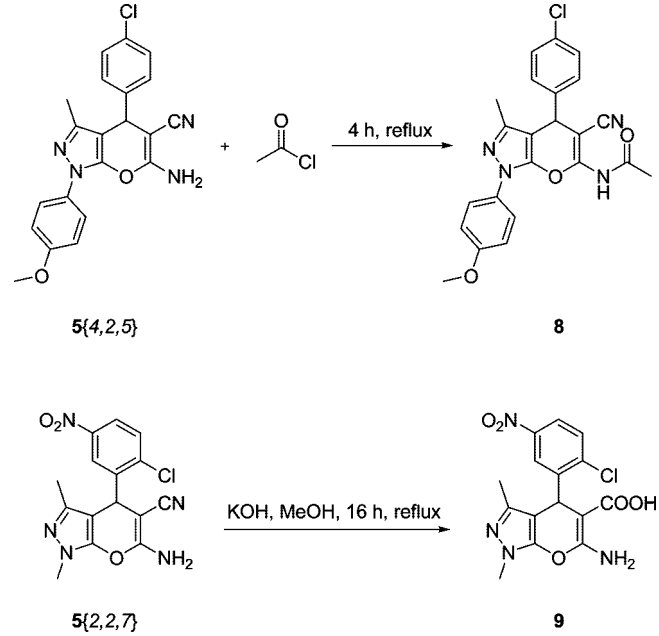
Scheme 3. Synthesis of Pyrano[2,3-*c*]pyrazol-6(1*H*)-one (**7**)



by HPLC. To achieve greater diversity other reactive methylene compounds, such as alkyl malonates, alkyl cyanoacetates, or cyanothioacetamide, can be used in this type of reaction.[9] Another advantage of this synthetic route is the use of chemset **3** contaminated with starting material because all the materials are soluble in ethanol except for the resulting 1,4-dihydropyrano[2,3-*c*]pyrazoles **5**. To evaluate the extension of the method from aldehydes to ketones, we synthesized 6-amino-3,4-dimethyl-4-(3-nitrophenyl)-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile **6** in good yield starting from 1-(3-nitrophenyl)ethanone, a reactive ethanone derivative, instead of an aldehyde (Scheme 2). According to the known method,[24] we prepared **7** (Scheme 3) to achieve an aromatization of the pyran ring system, which may be necessary for the three-dimensional orientation of the residue in our design of kinase inhibitors. To increase diversity of the 1,4-dihydropyrano[2,3-*c*]pyrazole scaffold, we acetylated the 6-amino group of derivative **5**{*4*,*2*,*5*} (Scheme 4). Furthermore, the 5-cyano group of **5**{*2*,*2*,*7*} can be saponified to yield compound **9** and shows the possibility of a subsequent functionalization of the 1,4-dihydropyrano[2,3-*c*]-pyrazole ring system.

In summary, an efficient synthetic route was applied in solution-phase parallel synthesis to prepare a library of diverse dihydropyrano[2,3-*c*]pyrazoles. All the proposed reactions allowed the preparation of products in good yield without further purification. The reaction products were prepared in moderate to average yield, even with different substituted aldehydes. We showed the possibility to extend the method from aldehydes to ketones. In some examples, the possibilities for diversification were demonstrated. Given that a multitude of hydrazines, β-keto esters, and

Scheme 4. Possible Derivatizations of Dihydropyrano[2,3-*c*]pyrazoles **5**



aldehydes are easily available, the method described could be readily applied to prepare large dihydropyrano[2,3-*c*]pyrazole libraries. The strategy should amend existing methodologies to allow rapid investigation of this class of heterocycles.

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Supporting Information Available. Experimental procedures, spectroscopic data, and references for known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Balkenhohl, F.; von dem Bussche-Huennefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed.* **1996**, *35*, 2288–2337.
(2) El-Tamany, E. S.; El-Shahed, F. A.; and Mohamed, B. H. *J. Serb. Chem. Soc.* **1999**, *64*, 9–18.
(3) Ismail, Z. H.; Aly, G. M.; El-Degwi, M. S.; Heiba, H. I.; and Ghorab, M. M. *Egyp. J. Biot.* **2003**, *13*, 73–82.
(4) Zaki, M. E. A.; Soliman, H. A.; Hiekal, O. A.; and Rashad, A. E. *Z. Naturforsch. C* **2006**, *61*, 1–5.
(5) Abdelrazek, F. M.; Metz, P.; Metwally, N. H.; and El-Mahrouky, S. F. *Arch. Pharm.* **2006**, *339*, 456–460.
(6) Abdelrazek, F. M.; Metz, P.; Kataeva, O.; Jaeger, A.; and El-Mahrouky, S. F. *Arch. Pharm.* **2007**, *340*, 543–548.
(7) Foloppe, N.; Fisher, L. M.; Howes, R.; Potter, A.; Robertson Alan, G. S.; and Surgenor, A. E. *Bioorg. Med. Chem.* **2006**, *14*, 4792–4802.
(8) Otto, H. H. *Arch. Pharm.* **1974**, *307*, 444–447.
(9) Otto, H. H.; Schmelz, H. *Arch. Pharm.* **1979**, *312*, 478–486.
(10) Klokol, G. V.; Krivokolysko, S. G.; Dyachenko, V. D.; Litvinov, V. P. *Chem. Heterocycl. Compd.* **1999**, *35*, 1183–1186.
(11) Shi, D.; Mou, J.; Zhuang, Q.; Niu, L.; Wu, N.; Wang, X. *Synth. Commun.* **2004**, *34*, 4557–4563.
(12) Jin, T. S.; Wang, A. Q.; Cheng, Z. L.; Zhang, J. S.; Li, T. S. *Synth. Commun.* **2005**, *35*, 137–143.

(13) Zhou, J. F.; Tu, S. J.; Zhu, H. Q.; Zhi, S. J. *Synth. Commun.* **2002**, *32*, 3363–3366.
(14) Guo, S. B.; Wang, S. X.; Li, J. T. *Synth. Commun.* **2007**, *37*, 2111–2120.
(15) Ren, Z.; Cao, W.; Tong, W.; Jin, Z. *Synth. Commun.* **2005**, *35*, 2509–2513.
(16) Ghali, N. I.; Venton, D. L.; Hung, S. C.; Le Breton, G. C. *J. Org. Chem.* **1981**, *46*, 5413–5414.
(17) Meyer, K. G. *Synlett* **2004**, 2355–2356.
(18) Yuasa, Y.; Tsuruta, H.; Yuasa, Y. *Org. Process Res. Dev.* **1998**, *2* (6), 412–414.
(19) Mendes, E.; Vernieres, J. C.; Keane, P. E.; Bachy, A. Eur. Patent EP A1 346208, 19891213, 1989.
(20) Butler, D. E.; DeWald, H. A. *J. Org. Chem.* **1971**, *36*, 2542–2547.
(21) Tietze, L. F.; Brumby, T.; Pretor, M.; Remberg, G. *J. Org. Chem.* **1988**, *53*, 810–820.
(22) Dyachenko, V. D.; Chernega, A. N. *Russ. J. Gen. Chem.* **2005**, *75*, 952–960.
(23) Lehmann, F.; Schollmeyer, D.; Laufer, S. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2008**, *64*, o701.
(24) Khan, M. A.; Cosenza, A. G.; Ellis, G. P. *J. Heterocycl. Chem.* **1982**, *19*, 1077–1085.

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