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Microwave-assisted organocatalytic multicomponent Knoevenagel/hetero Diels–Alder reaction for the synthesis of 2,3-dihydropyran[2,3-*c*]pyrazoles

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ABSTRACT

A rapid protocol for the multicomponent microwave-assisted organocatalytic domino Knoevenagel/hetero Diels–Alder reaction (DKHDA) has been developed for the synthesis of 2,3-dihydropyran[2,3-*c*]pyrazoles. The reported procedure could be used for the fast generation of novel substituted 2,3-dihydropyran[2,3-*c*]pyrazoles with potential anti-tuberculosis activity.

During the course of a drug discovery program dedicated to the identification of new molecular scaffolds as potential anti-tuberculosis agents, our research group identified compound **1** (Fig. 1) as a promising hit for further optimization.[1] In order to expand our knowledge on the structure activity relationship (SAR) for this family of compounds, we became interested in the development of rigid analogues such as the 2,3-dihydropyran[2,3-*c*]pyrazole **2** (Fig. 1). Further studies revealed in fact the biological importance of a *p*-chlorophenyl moiety fixed in a 'syn' relative position with respect to the C3-methyl group.[2] The synthesis of compounds closely related to **2** via inverse-electron-demand hetero Diels–Alder (HDA) reaction[3] between 4-arylidene-5-pyrazolones (general structure **I**, Fig. 2) and substituted vinyl ethers, has been thoroughly investigated by Desimoni in the late seventies[4] and more recently by Tietze and co-workers.[5] According to these studies, it has been hypothesized that pyrazolones in the *Z*-configuration (**I**, characteristic for compounds having $R_1 \neq H$) do not give directly the 1,4-cycloaddition product but are thermally converted into the *E*-isomers (**II**) in order to allow the formation of the products (**III**) (Fig. 2).[6] The latter compounds were commonly obtained after long reaction times (2–7 days) as diastereoisomeric mixtures of cis and trans cycloadducts in a 1:1 ratio (when R_1 = Me, R_2 = Et).[6a] Accordingly, we became interested in the development of a time- and atom-efficient

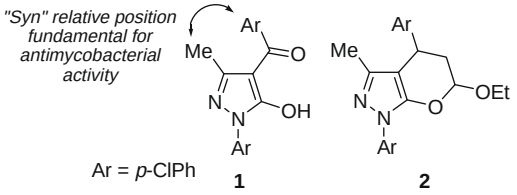

Figure 1. Hit compound **1** and the rigid target analogue **2**.

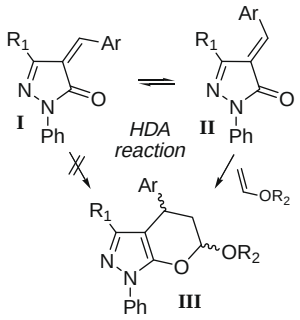

Figure 2.

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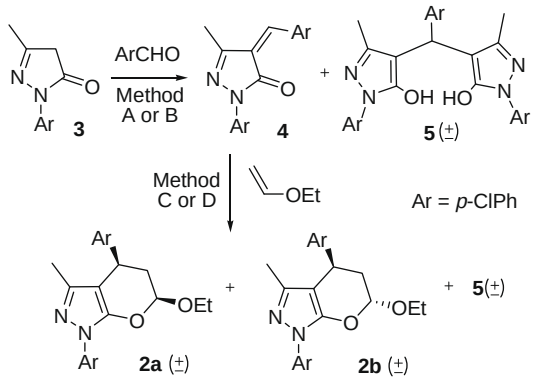


Scheme 1. Two-step procedure for the synthesis of **2**.

procedure for the preparation of rigid analogues such as the 2,3-dihydropyran[2,3-*c*]pyrazole **2** that could allow us to quickly produce novel analogues to be screened as anti-tuberculosis agents (Fig. 1). In this context, multicomponent reactions (MCRs) are particularly appealing, since they provide a practical access to complex polycyclic products in a single step by simultaneous reactions of three or more reagents, and allow to easily achieve substituent diversity of the core structure by varying each component.[7] We decided to combine the advantage of MCRs with that of microwave assisted technique and organocatalysis in order to speed up the synthesis of 2,3-dihydropyran[2,3-*c*]pyrazoles such as **2**.[8] The latter compound can in fact be seen as the product of a two step protocol starting with a Knoevenagel condensation between a pyrazol-2-one (**3**) and the opportune aldehyde, followed by a HDA reaction with ethylvinyl ether (EVE). While the Knoevenagel condensation is known to be catalyzed by both acids and bases, the Hetero Diels–Alder reaction can be accelerated by Lewis acids or hydrogen bond coordination with the heterodiene carbonyl group.[9] Accordingly, an organic compound bearing functional groups able to catalyze both synthetic steps could be favorably employed in a MCR for the synthesis of 2,3-dihydropyran[2,3-*c*]pyrazoles such as **2**. Moreover, considering that the thermal *Z*/*E* conversion of dienophiles **I** seems to be essential for the outcome of the HDA reaction, microwave irradiation could be used to additionally boost the formation of the desired product.[10] Herein we report a straightforward protocol for the microwave-assisted organocatalytic multicomponent Knoevenagel/hetero Diels–Alder reaction (KHDA) applied to the synthesis of 2,3-dihydropyran[2,3-*c*]pyrazoles (see Scheme 1).

Table 1
Optimizing the Knoevenagel condensation multicomponent

Entry	Method	Solvent	Temp (°C)	Time (min)	**4**[c] (%)	**5**[c] (%)
1	A[a]	—	130	40	87	5
2	B[b]	—	110	3	32	38
3	B[b]	EtOH	110	3	41	50

[a] Conventional heating.
[b] Microwave heating; reactions were conducted in a sealed tube.
[c] Determined by chiral HPLC–MS using an (*S*,*S*)-Whelk-O1 column (methanol/formic acid (0.05%) 85:15, flow rate 1.0 mL/min, UV-254 nm).

Initially, each step of the KHDA was studied independently. Dienophile **4** (the *Z*-configuration was confirmed by NOE experiments) was synthesized in good yields by heating pyrazolone **3** (1.5 equiv) with *p*-chlorobenzaldehyde (3 equiv) under neat conditions[11] at 130 °C while the use of microwave irradiation always increased the formation of the side-product **5** (resulting from the Michael addition of compound **3** on the activated double bond of **4**)[12] (Table 1). The HDA reaction of compound **4** with EVE under different reaction conditions (see Table 2) was then investigated in order to identify the more efficient experimental procedure both in terms of yields and diastereoisomeric excess. After an initial reaction conducted according to the standard HDA protocol (Table 2, entry 1), which led to the formation of pyranes **2a–b** in 1/1 ratio, several different microwave-assisted protocols were investigated. Compound **4** and EVE were reacted in different solvents (Table 2, entries 2–7)

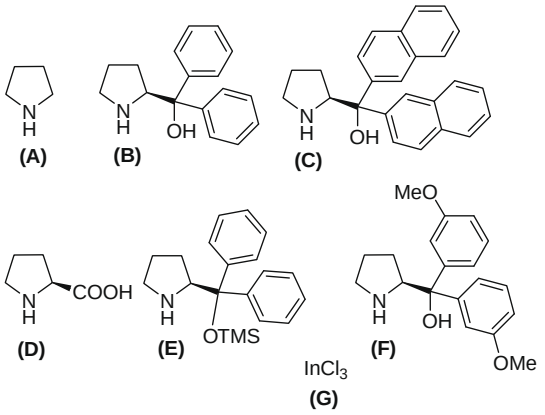
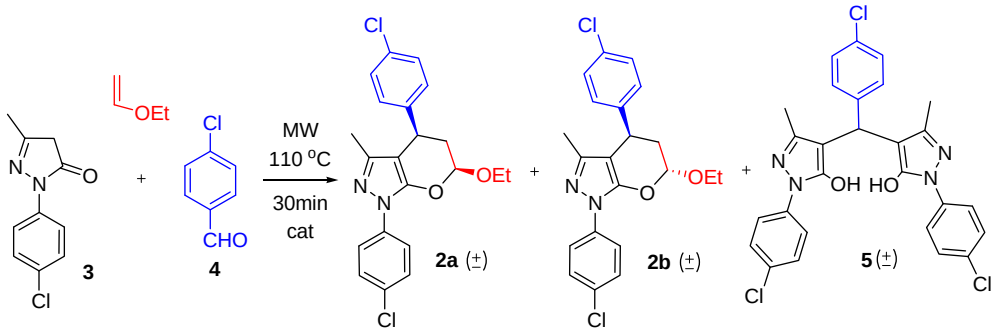


Figure 3. Catalysts.

Table 2
Optimizing the HDA reaction

Entry	Solvent	Method	Time (h)	**2a**[c] (%)	**2b**[c] (%)	**4**[c] (%)	**5**[c] (%)	Cat[d]
1	—	C[a]	48	38	31	—	—	—
2	MeOH	D[b]	0.5	20	13	62	—	—
3	EtOH	D[b]	0.5	6	2	86		—
4	^{t}BuOH	D[b]	0.5	41	12	35	—	—
5	CH_3CN	D[b]	0.5	4	3	92	—	—
6	DME	D[b]	0.5	15	7	77	—	—
7	Toluene	D[b]	0.5	—	—	100	—	—
8	^{t}BuOH	D[b]	0.5	24	8	—	48	A
9	^{t}BuOH	D[b]	0.5	67	19	—	9	B
10	^{t}BuOH	D[b]	0.5	47	10	11	26	E
11	DME	D[b]	0.5	30	11	24	17	A
12	DME	D[b]	0.5	52	26	10	5	B
13	DME	D[b]	0.5	42	21	18	8	E

[a] Conventional heating, 80 °C; reaction was conducted in a sealed tube.
[b] Microwave heating, 110 °C; reactions were conducted in a sealed tube.
[c] Determined by chiral HPLC–MS using an (*S*,*S*)-Whelk-O1 column (methanol/formic acid (0.05%) 85:15, flow rate 1.0 mL/min, UV-254 nm).
[d] All the catalysts were used in 20 mol % amount.



Scheme 2. Microwave-assisted organocatalytic multicomponent Knoevenagel/hetero Diels–Alder reaction (KHDA).

Table 3
Optimizing the DKHDA reaction

Entry	Solvent	Catalyst[a]	**2a**[b] (%)	**2b**[b] (%)	**5**[b] (%)	Ratio **2a**:**2b**
1	^{t}BuOH	—	—	—	Trace	—
2	^{t}BuOH	B	56[c]	12[c]	18	4:1
3	^{t}BuOH	C	56	15	23	4:1
4	^{t}BuOH	D	20	6	42	4:1
5	^{t}BuOH	E	32	8	54	4:1
6	^{t}BuOH	F	27	8	41	4:1
7	^{t}BuOH	G	11	7	—	1.5:1
8	MeOH	—	—	—	Trace	—
9	MeOH	B	42	27	27	1.5:1
10	MeOH	C	50[c]	33[c]	4	1.5:1
11	MeOH	D	27	19	51	1.5:1
12	MeOH	E	33	20	43	1.5:1
13	MeOH	F	32	18	38	1.5:1
14	MeOH	G	—	—	78	—
15	DME	—	—	—	Trace	—
16	DME	B	45[c]	15[c]	4	2.3:1
17	DME	C	38	19	34	2.3:1
18	DME	D	30	14	49	2.3:1
19	DME	E	18	6	36	3:1
20	DME	F	24	10	60	2.3:1
21	DME	G	10	12	—	1.2:1
22	—	B	21	9	52	2.3:1

[a] All the catalysts were used in 20 mol % amount.
[b] Determined by chiral HPLC–MS using an (*S*,*S*)-Whelk-O1 column (methanol/formic acid (0.05%) 85:15, flow rate 1.0 mL/min, UV-254 nm).
[c] Isolated yield.

at 110 °C under microwave irradiation for 30 min thus allowing us to select the best protic and aprotic solvents (^{t}BuOH and DME, entries 4 and 6) to be used next in combination with different organocatalysts (Table 2, entries 8–13). All the reactions were analyzed via HPLC–MS in order to quickly select the best reaction parameters for further optimizations. The organocatalyst to be used in the HDA reaction should possess one or two hydrogen donor moieties[13] (to activate the carbonyl group of the heterodiene) and a secondary amine moiety for iminium catalysis of the Knoevenagel reaction in the final multicomponent KHDA procedure. Accordingly, we combined the two solvents selected above with the organocatalysts **A**, **B,** and **E** reported in Figure 3 (Table 2, entries 8–13). The use of these catalysts demonstrated the important role played by the hydrogen bond coordination of the catalyst in accelerating the HDA reaction. In fact, while the HDA reactions in ^{t}BuOH (Table 2, entries 8–10) always gave the desired products **2a** and **2b** in high yields (probably due to additional coordination with the solvents), the reactions in DME (Table 2, entries 11–13) led to **2a** and **2b** in lower yield but allowed us to prove the importance of the sole catalyst in accelerating the HDA reaction (compare entry 6 with entries 11–13). In addition, while the carbonyl activation by double hydrogen bond (catalyst **B**) gave the best results both in terms of yields and diastereomeric excess (Table 2, entries 9 and 12), the *O*-TMS-protected catalyst **E** showed minor efficiency due to the loss of a hydrogen-donor moiety. The pyrrolidine catalyst **A** probably catalyzed a retro-Knoevenagel reaction,[14] which resulted in an increase of the side-product **5**. Once the usefulness of diaryl-prolinol derivatives in the catalysis of the microwave-assisted HDA reaction was verified, we applied the same reaction conditions to the multicomponent KHDA reaction. In a classical procedure, a mixture of pyrazolone **3** (1 equiv), aldehyde **4** (1 equiv), and EVE (10 equiv) was irradiated at 110 °C for 30 min in the presence of the opportune catalyst (Scheme 2, Table 3). Apart from pyrrolidine, which showed the increase in the formation of the side-product **5**, a series of catalysts (**B**–**G**, Fig. 3) were used in the multicomponent KHDA reaction: diaryl-prolinols **C** and **F** were used in order to analyze how the functionalization of the aryl moiety could influence the yields and diastereomeric excess. The commonly used L-proline (**D**) and the lewis acid indium-chloride (**G**) were also introduced in order to have a wider picture of the catalyst's effect. The results reported in Table 3 highlight the importance of the catalyst both for the Knoevenagel reaction between **3** and **4** and the next HDA reaction with EVE: as shown in entries 1, 8, and 15. In the absence of the catalyst the reaction did not start at all, while the best results were obtained. in the presence of diaryl-prolinols **B** and **C**. Neat reaction conditions (Table 3, entry 22) were not appropriate for this multicomponent KHDA protocol, giving high yields of the side-product **5**. Once more, the importance of the double hydrogen bond coordination for the carbonyl activation was also proved by the lower yields obtained with the *O*-TMS protected catalyst **E** and the deactivated catalyst **F** bearing electron releasing *m*-OMe groups on the aryl moieties. L-Proline, gave high yields of the side-product **5** while $InCl_3$ gave unsatisfactory results, even if outcome was different, regardless of the solvent used.

In summary, an efficient multicomponent microwave-assisted KHDA protocol for the synthesis of 2,3-dihydropyran[2,3-*c*]pyrazoles has been developed. Using the diaryl-prolinol catalyst **B** and ^{t}BuOH as the solvents, it was possible to obtain the desired compounds **2a** and **2b** in good yields (56% and 12%, respectively) and improved diastereoisomeric ratio (4:1) compared to the results previously obtained for similar compounds. The exploitation of this procedure will allow us to quickly synthesize novel rigid analogues of compound **1** as potential antitubercular agents.

Acknowledgments

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