Organocatalyzed and Uncatalyzed C=C/C=C and C=C/C=N Exchange Processes between *Knoevenagel* and Imine Compounds in Dynamic Covalent Chemistry

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Molecular diversity generation through reversible component exchange has acquired great importance in the last decade with the development of dynamic covalent chemistry. We explore here the recombination of components linked by C=C and C=N bonds through reversible double-bond formation, and cleavage in C=C/C=C and C=C/C=N exchange processes. The reversibility of the *Knoevenagel* reaction has been explored, and C=C/C=C C/C exchanges have been achieved among different benzylidenes, under organocatalysis by secondary amines such as L-proline. The substituents of these benzylidenes were shown to play a very important role in the kinetics of the exchange reactions. L-Proline is also used to catalyze the reversible C=C/C=C exchange between *Knoevenagel* derivatives of barbituric acid and malononitrile. Finally, the interconversion between *Knoevenagel* derivatives of dimethylbarbituric acid and imines (C=C/C=N exchange) has been studied and was found to occur rapidly in the absence of catalyst. The results of this study pave the way for the extension of dynamic combinatorial chemistry based on C=C/C=C and C=C/C=N exchange systems.

1. Introduction. – 'Constitutional Dynamic Chemistry' (CDC) [1] involves the dynamic recombination of molecular components linked through either non-covalent interactions or reversible covalent bonds. In recent years, the latter, dynamic covalent chemistry (DCC), has emerged as a powerful approach to create dynamic libraries of compounds of increasing structural diversity. The screening of these 'Dynamic Covalent Libraries' (DCLs) provides new perspectives in drug design [2] and material sciences [3] (for dynamic materials, see [4]). Representative examples of reversible reactions compatible with the DCC concept include amine/carbonyl condensations [5][6], transesterifications [7], disulfide exchange [8], peptide exchange [9], boronic ester formation [10], olefin metathesis [11], and *Diels–Alder* condensation [12]. However, there is a constant need for new reversible reactions to create DCLs of increased structural and chemical diversity, and complexity.

Organocatalysis [13] by primary and secondary amines *via* enamine and iminium intermediates has been actively pursued in recent years to facilitate carbonyl condensation processes such as *Knoevenagel* and aldolization reactions [14]. The *Knoevenagel* reaction consists in the condensation of an activated hydrogen compound such as β-keto esters and malonates with aldehydes or ketones [15a] (for an excellent review, see [15b]) in the presence of primary or secondary amines, resulting in the formation of a C=C bond. Most frequently employed secondary amine catalysts include

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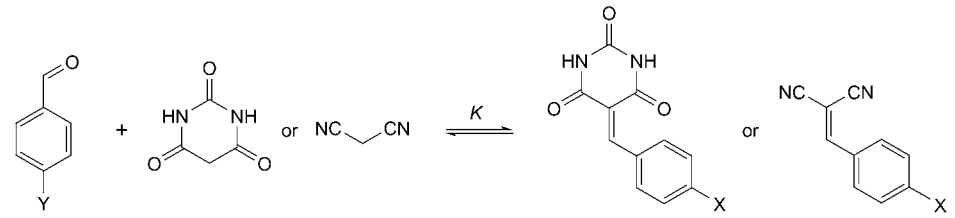
piperidine, sarcosine, and proline and its derivatives, the latter being extensively used for asymmetric organocatalysis [13].

In the present study, we have investigated the DCC processes involving reversibility and component exchange in *Knoevenagel* reactions through cleavage and reformation of C=C bonds between the condensation compounds of barbituric acid **B** or malononitrile **M**, and three benzaldehydes **1a**–**1c** (*Scheme 1*). We also explored the ability of selected secondary amines to catalyze these reactions, in particular using L-proline as the catalyst. Such processes amount to dynamic formation and cleavage of C,C double bonds, C=C, and allow for C=C/C=C exchange of either moiety. The exchange of components has been reported in *Michael* reactions on benzylidene compounds [16].

Scheme 1. *Benzaldehyde Derivatives* **1a**–**1c** *and Their* Knoevenagel *Condensation Compounds with Barbituric Acid* (**B**)*,* **2a**–**2c***, and Malononitrile* (**M**)*,* **3a**–**3c**



1a Y = Me_2N
1b Y = H
1c Y = NO_2

B

M

2a X = Me_2N
2b X = H
2c X = NO_2

3a X = Me_2N
3b X = H
3c X = NO_2

We have reported earlier *Knoevenagel*/imine (C=C/C=N) cross-exchange processes using L-proline as an organocatalyst [17] in pure (D_6)DMSO. As an extension of this previous work, we also describe here the C=C/C=N cross-exchange with *Knoevenagel* compounds of dimethyl-barbiturate, achieving fast recombination in the absence of catalyst in pure $CDCl_3$.

2. Results and Discussion. – 2.1. *Synthesis and Hydrolysis of the Benzylidene Compounds* **2a**–**2c** *and* **3a**–**3c** (*Scheme 1*). A series of benzylidene derivatives, **2a**–**2c** and **3a**–**3c**, were synthesized *via Knoevenagel* condensation between, respectively, barbituric acid **B** and malononitrile **M**, and 4-(dimethylamino)benzaldehyde (**1a**), benzaldehyde (**1b**), 4-nitrobenzaldehyde (**1c**). The reversible formation and hydrolysis processes of these compounds are illustrated in *Scheme 1*. They were followed by ^{1}H-NMR spectroscopy (see *Exper. Part*) in the presence of a secondary amine (L-proline, L-proline methyl ester, piperidine). Such bases, especially L-proline, accelerated both the rates of formation and of hydrolysis of the compounds. The corresponding kinetic (half-life, $t_{1/2}$) and thermodynamic equilibrium parameters (equilibrium constants K and corresponding free energies ΔG°) are compiled in *Table 1*.

Table 1. *Kinetic and Equilibrium Thermodynamic Parameters for* Knoevenagel *Condensation and Hydrolysis Processes*[a]). Half-life, $t_{1/2}$; +, reaction too fast; –, reaction too slow to determine the parameter, F = formation, H = hydrolysis, K = equilibrium constant and $\Delta G^\circ = -RT\ln(K)$.

	2a		**2b**		**2c**		**3a**		**3b**		**3c**	
Catalyst[b])	B	Pr	B	Pr	B	Pr	B	Pr	B	Pr	B	Pr
$t_{1/2}$ [h] F	4	1	20	2	4.5	2.1	–	3	+	+	+	+
$t_{1/2}$ [h] H	15	0.4	20.5	0.2	+	+	–	+	+	+	3	0.7
%[c]) F	77	82	57	59	62	61	–	95	95	95	91	91
%[c]) H	77	78	55	53	61	59	94	95	89	88	86	86
K	0.58	1.01	0.12	0.14	0.17	0.16	–	15.2	15.2	15.2	40.4	40.4
ΔG^0 [kJ mol^{-1}]	1.35	– 0.02	5.25	4.87	4.39	4.54	–	– 6.74	– 6.74	– 6.74	– 9.16	– 9.16

[a]) Experiments were performed at 60° in (D_6)DMSO/D_2O 99 : 1 with 10 mol-% base catalyst. [b]) B, blank; Pr, L-proline. [c]) %, Percentage of constituents at equilibrium. [d]) ΔG° in kJ mol^{-1}.

The equilibrium constants were obtained from the amounts of reactants and products according to *Eqn. 1*:

$$K = [\mathbf{2}]/[\mathbf{1}][\mathbf{B}] \text{ or } K = [\mathbf{3}]/[\mathbf{1}][\mathbf{M}] \quad (1)$$

The electrophilic behavior of the benzylidene derivatives **2** and **3** is strongly dependent on the nature of the probe-head (*i.e.*, **B** or **M**). Most reactive are the benzylidene derivatives whose probe-head is the strongest electron-withdrawing group and has the lowest pK_a. Thus, diethyl benzylidenemalonates (pK_a (diethyl malonate) = 16.4) proved to be less reactive than the benzylidene-malononitrile (pK_a (malononitrile) = 11.1) and much less reactive than the barbituric acid analogs (pK_a (barbituric acid) = 4.0), consistent with a recent study [16]. Because of the very low reactivity of diethyl benzylidenemalonates, we decided to focus our study on the barbiturate and malononitrile derivatives only. The stability of the benzylidene derivatives toward hydrolysis also proved dependent on the nature of the *para*-substituent on the benzaldehyde component. The compounds bearing electron-donating substituents such as dimethylamino (Me_2N), *i.e.*, **2a** and **3a**, were less reactive than those bearing an electron-attracting substituent (NO_2), **2c** and **3c**.

The effects of the addition of a base during the synthesis (formation) or hydrolysis of each benzylidene derivative were also examined. The reactions between 1 equiv. of aldehyde **1a** – **1c** and 1 equiv. of either barbituric acid **B** or malononitrile **M** (12.8 mM each) were carried out in (D_6)DMSO/D_2O 99 : 1 and at 60°, in the presence and in the absence of base as a potential catalyst (L-proline, L-proline methyl ester, or piperidine), and the formation of the corresponding conjugated benzylidene derivative was monitored by ^{1}H-NMR. The reverse (hydrolysis) reactions were performed in parallel, and the hydrolysis of each separately prepared conjugated benzylidene derivative (12.8 mM in (D_6)DMSO/D_2O 99 : 1 at 60°, in the presence and in the absence of base) was monitored by ^{1}H-NMR. After 36 h, the same distribution of all reaction components was observed for both forward (condensation) and backward (hydrolysis) processes, thus evidencing that the reactions were reversible and under thermodynamic control.

The effects of the addition of base on the kinetics and thermodynamics of the reaction were also investigated. Generally, all three bases tested (see *Fig. 1*) were found to accelerate both the synthesis and, conversely, the hydrolysis of the conjugated benzylidene compound. Of the three bases tested, L-proline proved the most efficient catalyst, followed by L-proline methyl ester. Piperidine came last despite its higher basicity, possibly because of extensive protonation. These results indicate the likely participation of L-proline carboxylic acid in the catalytic mechanism [18]. The most pronounced effects were observed for the formation and hydrolysis of compound **2b** with a Me_2N substituent (*Fig. 1*) for which L-proline accelerated the reaction tenfold ($t_{1/2}$ reduced from 20 to 2 h) when compared to the reaction carried out in the absence of base. It is also noteworthy that the catalytic effect of L-proline was lower for benzylidenes substituted with an electron-withdrawing group. In fact, such compounds hydrolyze quickly even in the absence of base, thus catalyst addition has little effect.

2.2. *Study of the* Knoevenagel *Exchange Reaction.* The reversibility of the *Knoevenagel* reaction involves hydrolytic cleavage of the C=C bond by a *retro-Knoevenagel* process. It can be ascertained by the addition of another aldehyde component to produce a new benzylidene conjugate with C=C bond interchange (*Scheme 2*), *via* a sequential hydrolysis–condensation mechanism. The capacity of various benzylidene derivatives to undergo such exchange reactions in the presence of various aldehydes was investigated, in the absence or in the presence of different secondary amines, L-proline, L-proline methyl ester or piperidine as potential catalysts, for all possible combinations of one benzylidene derivative (*i.e.*, **2a**–**2c** and **3a**–**3c**) with one aldehyde (*i.e.*, **1a**–**1c**; *Scheme 2*). Each benzylidene compound (12.8 mM) was solubilized in $(D_6)DMSO/D_2O$ 99:1, heated at 60° together with 1 equiv. of a differently substituted aldehyde, and in the absence or in the presence of one of the three bases. For each reaction, the percentage of each component of the reaction mixture (aldehydes and benzylidene derivatives) as a function of time, as well as the initial rates of disappearance of the starting benzylidene compound were determined by ^{1}H-NMR spectroscopy. The reactions were also carried out at 25° and 40°, but the

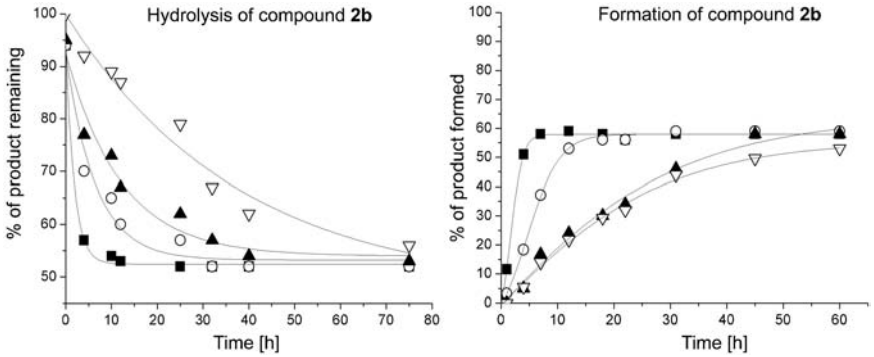


Fig. 1. *Formation* (left) *and hydrolysis* (right) *of compound* **2b** *catalyzed by secondary amines.* ▽, No base added; ▲, piperidine; ○, L-proline methyl ester; ■, L-proline. Reactions were carried out in triplicate, and the standard deviation was < 5%. The curves were drawn through the experimental points for clarity.

exchange became very slow (roughly three times slower at 40°). The results are compiled in *Table 2* and *Fig. 2*.

First, reactions were carried out starting from a benzylidene derivative of barbituric acid and a given aldehyde. In all cases, aldehyde exchange was observed even in the absence of a secondary amine base. However, addition of 10 mol-% molar of a base increased significantly the exchange kinetics. For instance, the half-life for exchange, $t_{1/2}$, was reached up to 85 times faster upon addition of L-proline, compared to the control experiment without added base (reaction between **2a** and **1b**; *Table 2* and *Fig. 2*). For the same reaction, piperidine reduced $t_{1/2}$ by a factor of 2 only. There was almost no effect with **2c** from 4-nitrobenzaldehyde (**1c**), because the hydrolysis was already very fast, in the absence of base. The benzylidene compounds formed from benzaldehyde (**1b**) and 4-(dimethylamino)benzaldehyde (**1a**) were much more sensitive to base catalysis.

Next, similar reactions were carried out starting from benzylidene derivatives of malononitrile (**M**; *Table 2*, *Entry 4*). L-Proline was again the most efficient catalyst. For the exchange reaction between **3b** and **1c**, it accelerated the reaction 2.5 times. Piperidine also accelerated the reactions, notably for the reaction between **3c** and **1b** (threefold compared to the blank). No exchange was observed over 55 h when starting from compound **3a**, which can be explained by its very low reactivity towards hydrolysis even in presence of catalytic amounts of L-proline.

The mechanism of the catalysis of the *Knoevenagel* exchange reaction by a secondary amine may be considered to involve addition on the benzylidene conjugate leading to an iminium intermediate by an addition–elimination process, followed by condensation of the released barbiturate or malonate anion with the added aldehyde (*Scheme 3*). This catalytic cycle of proline-catalyzed reactions has been extensively

Scheme 2. *Reversible* Knoevenagel *Reactions Involving Exchange of the Aldehyde Moiety between a Benzylidene Derivative of Barbituric Acid,* **2a**–**2c** (*top*)*, and a Malononitrile,* **3a**–**3c** (*bottom*)*, and a* para-*Substituted Benzaldehyde,* **1a**–**1c**

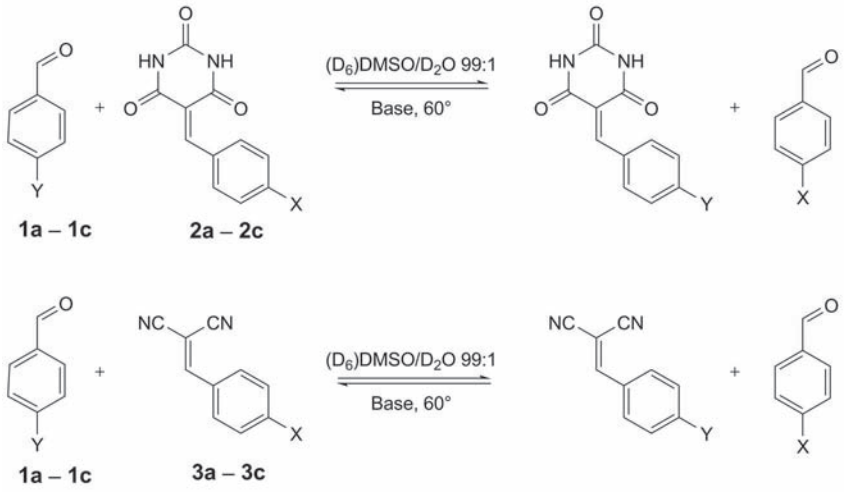


Table 2. *Kinetic and Equilibrium Thermodynamic Parameters for the* Knoevenagel *Exchange Reaction between Benzylidene Compounds* **2a**–**2c** *or* **3a**–**3c** *and the Aldehydes* **1a**–**1c**. Half-life $t_{1/2}$. Proportions [%] of the different compounds at equilibrium in (D_6)DMSO/D_2O 99 : 1 at 60°

Entry	Reaction	[a])	Compound distribution [%]					$t_{1/2}$ [h]	K_b [b])	K_c [c])	ΔG_b° [b])	ΔG_b° [b])
1			**2a**	**1b**	**2b**	**1a**	**B**					
	2a + **1b**	f_b	49	15	16	8	12	85	0.18	0.18	4.25	4.25
		f_c	49	15	16	9	12	1				
	2b + **1a**	r_b	49	16	17	9	12	80				
		r_c	49	15	14	9	13	8				
2			**2a**	**1c**	**2c**	**1a**	**B**					
	2a + **1c**	f_b	31	27	9	10	23	36	0.11	0.12	5.47	5.25
		f_c	32	25	9	11	22	20				
	2c + **1a**	r_b	31	27	9	11	23	39				
		r_c	32	26	9	11	23	10				
3			**2b**	**1c**	**2c**	**1b**	**B**					
	2b + **1c**	f_b	29	17	27	14	13	51	0.80	0.86	0.55	0.37
		f_c	29	16	29	13	12	4				
	2c + **1b**	r_b	31	15	30	13	11	22				
		r_c	31	15	30	14	11	4				
4			**3b**	**1c**	**3c**	**1b**	**M**					
	3b + **1c**	f_b	29	22	21	15	13	5	0.56	0.53	1.44	1.57
		f_c	29	21	21	16	13	2				
	3c + **1b**	r_b	28	20	21	17	14	15				
		r_c	29	22	22	15	12	4				

[a]) f_b, Forward reaction without catalyst; f_c, forward reaction with catalyst 10 mol-% L-proline; r_b, reverse (backward) reaction without catalyst; r_c, backward reaction with 10 mol% L-proline as catalyst. [b]) K_b, Equilibrium constant of the blank reaction. [c]) K_c, Equilibrium constant of the catalyzed reaction. [d]) $\Delta G_b^{\circ} = -RT \ln K_b$ [kJmol^{-1}]. [e]) $\Delta G_c^{\circ} = -RT \ln K_c$ [kJmol^{-1}].

documented in [18] (sequential hydrolysis, then condensation). Generally, L-proline methyl ester proved to be a less efficient catalyst than free proline, again evidencing participation of the carboxylic acid in the catalytic process. Although the secondary amine is the key moiety that is involved in the mechanism of the *retro-Knoevenagel* reaction, the iminium formed with the benzylidene derivative is likely to be stabilized by the neighboring carboxylate group, which cannot occur with the methyl ester analog.

2.3. *Organocatalysis of Benzylidene/Benzylidene C=C/C=C Cross-Exchange Processes.* Recently, we reported on the generation of DCLs involving imine/imine C=N/C=N and benzylidene/imine C=C/C=N exchange processes, and on exploiting L-proline as an organocatalyst [17]. To further extend the range of DCLs, we investigated the benzylidene/benzylidene C=C/C=C cross-exchange reaction between benzylidene-barbiturates, **2a**–**2e**, and differently substituted benzylidene-malononitriles, **3a**–**3e**, as depicted in *Scheme 4*. According to the previous results of the benzylidene/imine C=C/C=N exchanges [17], the benzylidene-barbiturates were easily hydrolyzed in

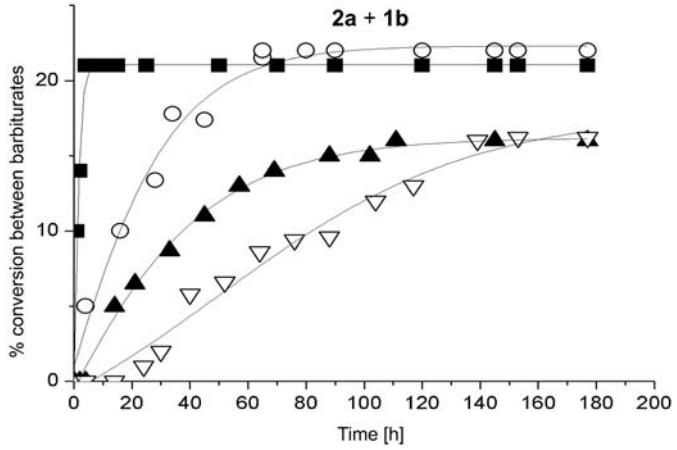
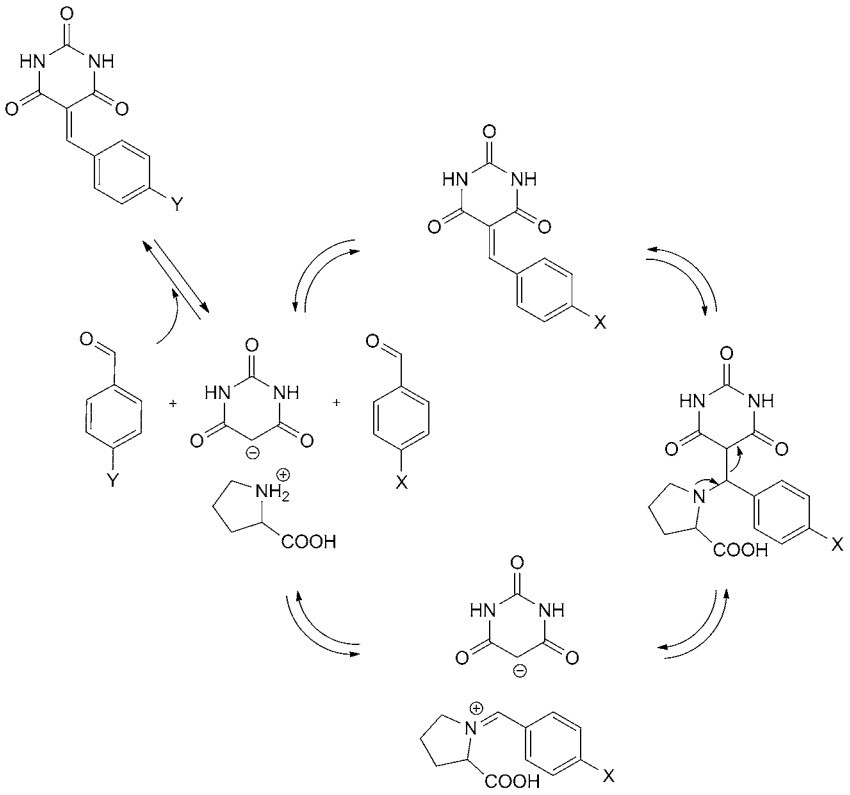
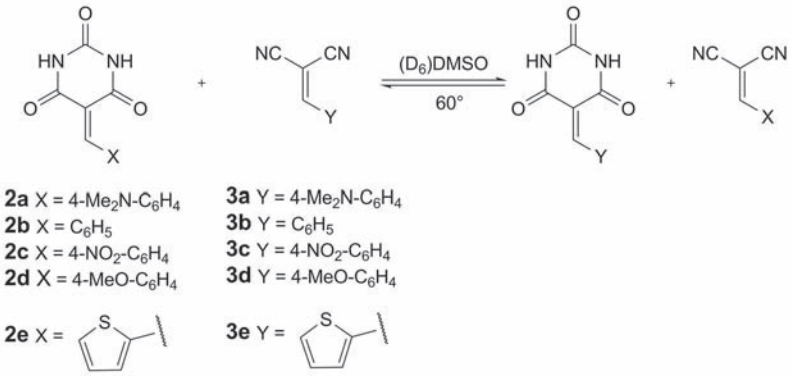


Fig. 2. *Secondary-amine catalyzed exchange reactions between* **2a** *and aldehyde* **1b**. ▽, No base; ▲, piperidine; ○, L-proline methyl ester; ■, L-proline. The reactions were carried out in triplicate and the standard deviation was $< 5\%$. The curves were drawn through the experimental points for clarity.

Scheme 3. *Mechanism of the Secondary Amine-Catalyzed* Knoevenagel *Aldehyde Exchange Reaction*



Scheme 4. *The C=C/C=C Cross-Exchange Reactions between Benzylidene-barbiturates* **2a**–**2e** *and Differently Substituted Benzylidene-malononitriles* **3a**–**3e** *in (D$_6$)DMSO at 60°*



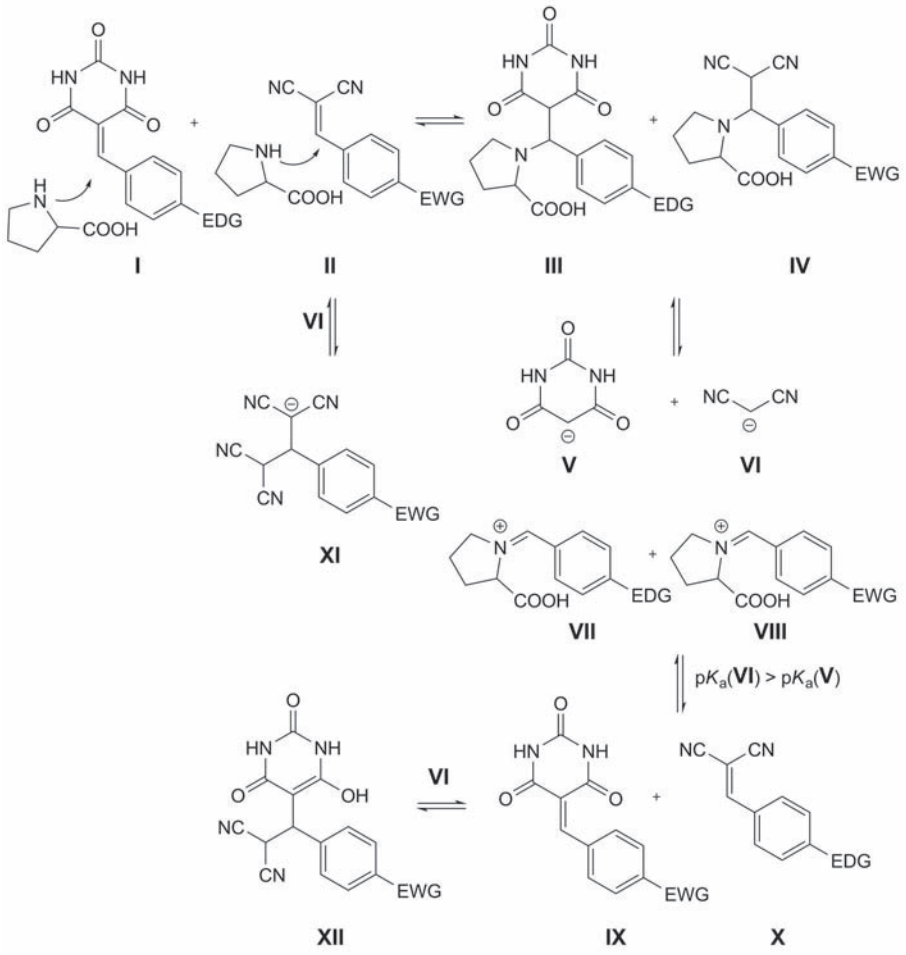
(D$_6$)DMSO/D$_2$O 99 : 1 solution, so that pure (D$_6$)DMSO (given as containing less than 0.02% of H_2O) was chosen as solvent. Therefore, the further exploration of benzylidene/benzylidene, C=C/C=C, exchanges were conducted in this solvent in order to minimize hydrolysis, which, however, cannot be fully avoided.

The reactions were carried out with stoichiometric amounts of benzylidene derivative (12.8 mM each) in pure (D$_6$)DMSO, as well as in the presence of 10% L-proline. The corresponding $t_{1/2}$ values and compound distributions of the final solutions are compiled in *Table 3*. Equilibrium parameters were not calculated, due to the occurrence of of hydrolysis to variable extents.

Here again, the efficiency of benzylidene exchange depended on the head-group substituent of both starting compounds acting as *Michael* acceptors. Considering first the pair of compounds **2a**, bearing electron-donating group (EDG), and **3c**, bearing an electron-withdrawing group (EWG), the cross-exchange reaction was expected to yield the products **2c** and **3a** (*Table 3*, *Entry 1*). The ^{1}H-NMR spectrum of the mixture after the start of the interchange reaction showed new signals at 4.73, 4.94, 5.32, 6.21, 7.26, 7.63, 7.76, 7.91, 9.50, and 12.2 ppm, which were assigned to be the *Michael*-type adducts **XI** and **XII** (*cf. Scheme 5*). In addition, the electrospray high-resolution mass spectrum (HR-ESI-MS) also supported the formation of adducts **XI** and **XII**, which correspond to the peaks at *m*/*z* 338.343 ($[(M+H+Na)+CH_3OH+H_2O]^+$) and 360.324 ($[(M+H)+CH_3OH]^+$), respectively. Neither adduct could be isolated. In the reaction mixture, the most reactive electrophiles [19] are **2c** and **3c**, so that they may react with the better nucleophile, the manolonitrile anion formed from **3c** (pK_a(**VI**) > pK_a(**V**)), affording adducts **XI** and **XII**. Thus, product **2c** was formed, but it was trapped as its *Michael*-type adduct **XII**. On the other hand, reaction of malononitrile with **3c** precludes the formation of the product **3a**. The possible mechanism of this cross-exchange reaction is outlined in *Scheme 5*.

The reversibility of this reaction was studied by combining **2c** and **3a** (*Table 3*, *Entry 2*). Both starting compounds were fully hydrolyzed, and the anticipated products **2a** and **3c** did not form even after 20 d, at which time decomposition of the compounds had occurred. This result indicated that hydrolysis precludes the recondensation to

Scheme 5. *Possible Mechanism of the Cross-Exchange Reaction between* Knoevenagel *Compounds, Following Sequential Hydrolysis/Condensation Steps* [18]



form **2a** and **3c** and thus the exchange reaction. For the same reason, no *Michael*-type adduct **XII** was observed.

Next, **2b** and **3c** were selected as starting compounds, both bearing EWGs (*Table 3*, *Entry 3*). These substrates were more suitable for the cross-exchange than the molecules exhibiting a large difference in their electrophilicity, *i.e.*, **2a** and **3c**, and both products **2c** and **3b** were formed. The hydrolysis products were observed in a less than 10% yield. In addition, the signals of the *Michael*-type adducts **XI** and **XII** were also detected in the ^{1}H-NMR spectrum of the mixture as characteristic *doublet*s at 4.94 and 5.32 ppm, attributed to **XI** (1%), and at 4.72 and 6.20 ppm, attributed to **XII** (9%), in agreement with reported values [20] and with MS data (see below). The reverse reaction was performed by mixing compound **2c** and **3b** (*Table 3*, *Entry 4*), and component **2b** and **3c** were obtained in comparable amounts as in the forward case,

Table 3. *Kinetic and Equilibrium Thermodynamic Parameters for* Knoevenagel *Cross-Exchange Reactions* (*Scheme 3*). Half-life, $t_{1/2}$; – = reaction too slow to determine the parameter. Proportions [%] of the different compounds in the C=C/C=C cross-exchange reaction between benzylidene-barbiturates and benzylidene-malononitriles in (D_6)DMSO at 60° **a**, 4-(dimethylamino)benzaldehyde; **b**, benzaldehyde; **c**, 4-nitrobenzaldehyde; **d**, 4-methoxybenzaldehyde; **e**, thiophene-2-carbaldehyde; **f**, 4-(dimethylamino)benzaldehyde hydrate; **g**, benzaldehyde hydrate; **h**, 4-nitrobenzaldehyde hydrate; **i**, 4-methoxybenzaldehyde hydrate; **j**, thiophene-2-carbaldehyde hydrate; **B**, barbiturate; **M**, malononitrile, and **XI** and **XII**, *Michael*-type adducts. All measurements were repeated three times. The reproducibility of the values obtained was ±2%.

Entry[a])	$t_{1/2}$ [h][b])	Reaction time [h][c])	Compound distribution [%][d])											
			Starting compound **2a** + **3c**											
			2a	**3c**	**2c**	**3a**	**a**	**c**	**f**	**h**	**B**	**M**	**XI**	**XII**
1b	50	164	35	30	5	11	1	6	–	–	3	3	–	6
1c	45	144	33	26	5	13	2	4	–	–	4	3	2	7
			Starting compound **2c** + **3a**											
			2c	**3a**	**2a**	**3c**	**a**	**c**	**f**	**h**	**B**	**M**	**XI**	**XII**
2b	n.a.	142	33	50	–	–	<1	12	<1	1	2	1	–	–
2c	n.a.	142	32	52	–	–	<1	9	<1	3	2	1	–	–
			Starting compound **2b** + **3c**											
			2b	**3c**	**2c**	**3b**	**b**	**c**	**g**	**h**	**B**	**M**	**XI**	**XII**
3b	8	53	16	10	22	31	1	7	<1	1	3	3	<1	5
3c	3	24	12	9	20	26	8	3	<1	2	5	5	1	9
			Starting compound **2c** + **3b**											
			2c	**3b**	**2b**	**3c**	**b**	**c**	**g**	**h**	**B**	**M**	**XI**	**XII**
4b	20	55	22	33	14	7	1	9	<1	2	3	3	–	5
4c	14	32	23	36	13	7	1	6	<1	2	3	3	–	5
			Starting compound **2a** + **3d**											
			2a	**3d**	**2d**	**3a**	**a**	**d**	**f**	**i**	**B**	**M**	**XI**	**XII**
5b	n.a.	23[e])	49	49	1	1	–	–	–	–	–	–	–	–
	n.a.	488[f])	35	37	12	12	2	1	–	–	<1	<1	–	–
5c	9	29	24	24	19	24	1	3	<1	1	2	<1	1	–
			Starting compound **2d** + **3a**											
			2d	**3a**	**2a**	**3d**	**a**	**d**	**f**	**i**	**B**	**M**	**XI**	**XII**
6b	n.a.	95[e])	48	49	1	<1	1	<1	–	–	–	–	–	–
	n.a.	533[f])	43	48	1	2	1	5	–	–	1	–	–	–
6c	30	98	23	30	19	19	<1	4	<1	1	3	<1	<1	–
			Starting compound **2e** + **3d**											
			2e	**3d**	**2d**	**3e**	**d**	**e**	**i**	**j**	**B**	**M**	**XI**	**XII**
7b	40	128	46	43	6	6	1	–	<1	–	–	<1	–	–
7c	2	6	43	40	6	7	2	–	<1	–	1	1	1	–
			Starting compound **2d** + **3e**											
			2d	**3e**	**2e**	**3d**	**d**	**e**	**i**	**j**	**B**	**M**	**XI**	**XII**
8b	180	532	8	8	42	40	2	–	–	–	1	<1	–	–
8c	2	6	6	8	42	39	3	–	–	–	1	1	1	–

[a]) b, Blank reactions, and c, catalyzed reaction with 10 mol-% L-proline as catalyst. [b]) Half-life; n.a., not applicable. [c]) Reaction time indicates the time when no further change in composition could be observed. [d]) Compound not observed; <1, only traces of product detected. [e]) The reaction started. [f]) The reaction did not reach equilibrium.

indicating that the reaction was reversible, and that the equilibrium had been more or less reached under thermodynamic control. In the reverse case, only *Michael*-type adduct **XII** was detected by ^{1}H-NMR which exhibited a OH signal at 12.18 ppm, and *doublet*s at 4.74 and 6.20 ppm, in 5% each under these conditions both in the presence and absence of L-proline. The formation of **XII** was also confirmed by HR-ESI-MS showing peaks at *m*/*z* 346.34 ($[M + H_3O]^+$).

Next compounds **2a** and **3d**, both bearing EDGs, were reacted (*Table 3*, *Entry 5*) to give **2d** (19%) and **3a** (24%) as products at equilibrium after *ca.* 29 h. The ^{1}H-NMR *doublet*s at 4.48 and 6.09 ppm, observed during the exchange process in the presence of L-proline, are characteristic of the *Michael*-type adduct **XI** (1%), whose formation, was confirmed by HR-MS data with peaks at *m*/*z* 287.21 ($[M + 2\ H_3O]^+$). The hydrolysis products in the presence of L-proline amounted to less than 4%. Equilibrium was reached after 29 h in the presence of L-proline, but, in its absence, the reaction was extremely slow, barely showing exchange after 23 h (1% each of the products **2d** and **3a**). Furthermore, after 20 d, **2d** and **3a** formed (12% each), indicating that the reaction in the absence of catalyst was extremely slow. Nevertheless, the uncatalyzed reaction did not afford any *Michael*-adduct, but gave a trace amount (1%) of hydrolysis products. The reverse reaction, starting with **2d** and **3a** (*Table 3*, *Entry 6*), furnished **2a** and **3d** in similar amounts as the forward reaction, and reached equilibrium after 98 h in the presence of L-proline. Again, in the absence of L-proline, the exchange reaction was significantly slower, with exchange products being formed in only a trace amount (*ca.* 1% each) after 4 d, with little change after 22 d where only **2a** (1%) and **3d** (2%) were observed. For both forward and back reactions (in the presence of L-proline), hydrolysis products were formed in yields of less than 4%.

Finally, the exchange reaction between **2e** and **3d** (*Table 3*, *Entry 7*), and the reverse reaction between **2d** and **3e** (*Table 3*, *Entry 8*) yielded the corresponding products in comparable amounts in the presence of L-proline. These reactions were faster than the other series of L-proline-catalyzed *Knoevenagel* cross-exchanges, approaching equilibrium after 6 h. In addition, the *Michael*-type adduct **XI** was observed in trace amount (1%) for both forward and reverse reactions (characteristic *doublet*s at 4.46 and 6.07 ppm in the ^{1}H-NMR spectrum). The HR-ESI-MS was used to confirm the formation of the addition product by showing corresponding peak at *m*/*z* 287.2 ($[M + 2\ H_3O]^+$). In the absence of L-proline, exchange products could only be observed after 23 h for both forward and reverse reaction. The equilibrium was approached after 128 and 532 h for forward and backward directions, respectively. Interestingly, the reaction in the absence of L-proline did not afford any *Michael*-type adducts, only the hydrolysis products formed. The hydrolysis products for both in presence and in absence of L-proline amounted to less than 2%. Under these conditions, L-proline demonstrated marked organocatalysis, as it accelerated the reaction from twofold (*Table 3*, *Entry 3*) up to *ca.* 89-fold (*Table 3*, *Entry 8*), when one compares the blank reaction at the same reaction time with the completed catalyzed reaction.

2.4. *Benzylidene/Imine, C=C/C=N, Exchange Process Involving 1,3-Dimethylbarbituric Acid*. The C=C/C=N interconversion was reported in our previous work [17], implementing *Knoevenagel* compounds formed from barbituric acid to achieve the cross-exchange in pure (D_6)DMSO. These reactions were accelerated by L-proline. Herewith, we extend these earlier studies and report the C=C/C=N cross-exchange

between *Knoevenagel* compounds derived from 1,3-dimethylbarbituric acid, **4a**–**4e**, and the same imine compounds, **5a**–**5e**, as previously used (*Scheme 6*). The solubility of the *Knoevenagel* compounds was screened in different solvents, and they were particularly very soluble in $CDCl_3$. The cross-exchange reactions could, therefore, be carried out in $CDCl_3$ (filtered prior to use through a column of basic alumina to remove HCl and avoid acid catalysis) with stoichiometric amounts of benzylidene-1,3-dimethylbarbituric acid derivatives and imine compounds (20 mM each). Both the forward and reverse reactions were followed by ^{1}H-NMR spectroscopy. In view of the fast rates of the exchange reactions, the rate constants could not be obtained, but the equilibrium constants were determined instead, as indicated in the *Exper. Part* and compiled in *Table 4*.

In one of the initial C=C/C=N cross-exchange experiments, **4a** and **5e** (*Table 4*, *Entry 1*), both bearing EDGs, were reacted in $CDCl_3$. After 68 min, the percentage of the exchange products **4e** and **5a** remained constant, indicating that equilibrium had been reached. When **4e** and **5a** were mixed under the same conditions, **4a** and **5e** were formed to give after 69 min a mixture containing the same relative percentages of all four compounds, thus confirming that the system was at thermodynamic equilibrium.

The first set of experiments in *Entry 1* of *Table 4* indicates that the interconversion of the *Knoevenagel* compound and an imine was facile and under thermodynamic control when the substrates both bear EDGs. We further explored the interconversion efficiency as a function of substrate electron affinity, choosing next compounds **4b**, bearing EDGs, and **5c**, bearing EWGs (*Table 4*, *Entry 2*). The interconversion products in $CDCl_3$, **4c** and **5b**, were formed immediately after mixing in a ratio that did not change after 2 min. In addition, the reverse reaction, determined by combining **4c** and **5b** under the same conditions, also furnished the products **4b** and **5c**. For this exchange pair, **4c** and **5b** were the favored products showing that the latter compounds are the most thermodynamically stable under these conditions. In this reaction, hydrolysis products were observed in the trace amount.

Next, we selected the substrates **4b** and **5e** for the forward reaction, and combined **4e** and **5b** for the reverse one (*Table 4*, *Entry 3*). The electron-donating properties of the substituent on **4b** were expected to be weaker than that on **4a** (*Table 4*, *Entry 1*).

Scheme 6. *The C=C/C=N Cross-Exchange Reactions Between Benzylidene-1,3-dimethylbarbituric Acids* **4a**–**4e** *and Imines* **5a**–**5e** *in $CDCl_3$ at Room Temperature*

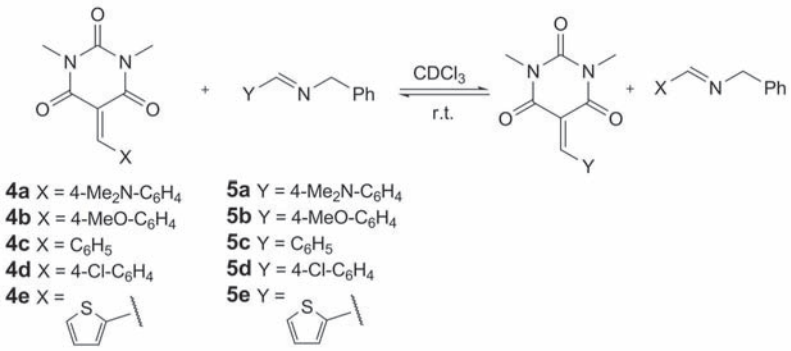


Table 4. *Proportions* [%] *of the Different Compounds in the C=C/C=N Cross-Exchange Reactions between Benzylidene-1,3-dimethylbarbituric Acids and Imines in $CDCl_3$ at Room Temperature.* **a**, 4-(dimethylamino)benzaldehyde; **b**, benzaldehydes; **c**, 4-nitrobenzaldehyde; **d**, 4-methoxybenzaldehyde; and **e**, thiophene-2-carbaldehyde

Entry	Starting compounds	Reaction[a])	Reaction time[b]) [min]	Compound distribution [%][c])							K_{eq}
				4a	**5e**	**4e**	**5a**	**a**	**e**	**f**	
1	**4a** + **5e**	f	68	22	21	28	29	< 1	–	–	2.45
	4e + **5a**	r	69	18	17	33	32	< 1	–	–	
				4b	**5c**	**4c**	**5b**	**b**	**c**	**f**	
2	**4b** + **5c**	f	2	13	14	37	36	< 1	< 1	–	7.32
	4c + **5b**	r	2	13	14	37	36	< 1	< 1	–	
				4b	**5e**	**4e**	**5b**	**b**	**e**	**f**	
3	**4b** + **5e**	f	60	6	4	44	45	–	–	–	92.05
	4e + **5b**	r	13	5	4	46	45	< 1	–	–	
				4b	**5a**	**4a**	**5b**	**a**	**b**	**f**	
4	**4b** + **5a**	f	11	9	7	43	42	< 1	–	–	30.43
	4a + **5b**	r	3	7	8	45	41	< 1	–	–	
				4d	**5a**	**4a**	**5d**	**a**	**d**	**f**	
5	**4d** + **5a**	f	11	5	4	46	45	< 1	< 1	–	152.79
	4a + **5d**	r	3	3	3	47	47	–	–	–	
				4d	**5b**	**4b**	**5d**	**b**	**d**	**f**	
6	**4d** + **5b**	f	3	14	14	37	35	< 1	< 1	–	7.31
	4b + **5d**	r	2	12	14	38	36	–	–	–	

[a]) f, Forward reaction; r, reverse reaction. [b]) Reaction time indicates the time when no further change in composition could be observed. [c]) Compound distribution values measured 4–5 times and averaged (standard deviation < 2%). –, Compound not observed; < 1, only traces of product detected.

The favored compounds at equilibrium were **4e** and **5b** as a result of the electronic effects of the substituents. In this case, for both forward and reverse reaction, the hydrolysis products formed in trace amount as well.

The substrates for the next experiment were **4b** and **5a** for the forward, and **4a** and **5b** for the reverse reaction (*Table 4*, *Entry 4*). The forward and reverse reactions reached equilibrium after 11 and 3 min, respectively. As compared to the reaction in *Entry 2*, **5a** has a higher electron donating ability than **5c**; therefore, the forward reaction in *Entry 4* was slightly slower than the one in *Entry 2*. Clearly, the efficiency of *Knoevenagel*/imine exchange depends on the electronic profile of both substrates.

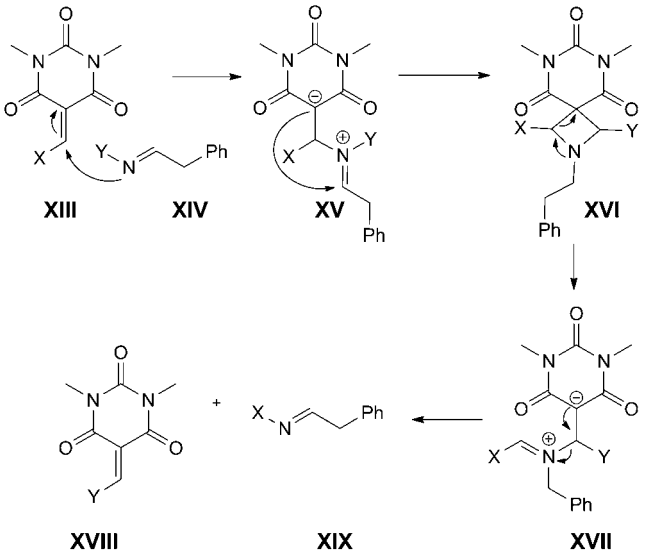
To explore the exchange reaction between substrates of markedly different electron affinities, a mixture of **4d** and **5a**, bearing EWGs and EDGs, respectively, was studied. Following mixing, the reaction again occurred immediately and reached equilibrium after 11 min, with only small amounts of the starting materials left (*ca.* 3%). Conversely, the backward reaction was performed by combining **4a** and **5d** to give **4d** and **5a** as the exchange products of 3% each at equilibrium. In addition, the favored

products at equilibrium were **4a** and **5d** for both forward and backward reaction under these conditions.

Finally, the reaction of substrates **4d** and **5b** (*Table 4*, *Entry 6*) was examined, where **5b** has lower electron-donating ability than **5a** (*Table 4*, *Entry 5*). The formation of the products **4b** and **5d** were instantaneously formed. The reverse reaction was performed by mixing **4b** and **5d**, also to give immediately **4d** and **5b**. Both forward and reverse reactions gave the same mixture of the four constituents, indicating that thermodynamic equilibrium has been reached immediately after mixing.

The cross-exchange reactions observed here may proceed, in principle, following two different mechanisms. A dissociation/recondensation process may well take place due to the presence of (unobservable) traces of H_2O, similarly to the reaction scheme of the proline-catalyzed reactions conducted in DMSO (*cf. Schemes 3* and *5*). On the other hand, the very fast exchange observed in $CDCl_3$, where no aldehyde could be detected, would indicate a mechanism of metathesis type, whereby the benzylidene-1,3-dimethylbarbituric acid would function as a neutral organic *Lewis* acid [20], while the imine would be able to act as neutral organic nucleophile. Such a metathesis-like mechanism of C=C/C=N interchange would involve the nucleophilic addition of the imine N-atom at the CH end of (ring)C=CH bond of the benzylidene-1,3-dimethylbarbituric acid to form the benzylidene-1,3-dimethyl barbituric acid–iminium adduct **XV** (*Scheme 7*), followed by internal cyclization to a four-membered azetidine ring intermediate **XVI**, which then could open to give either the starting compounds back, or the products **XVIII** and **XIX**, resulting from the cross-exchange of the components. In a related fashion, the formation of a four-membered carbocyclic intermediate has been found to occur in organocatalysis of *Michael* addition reactions of aldehydes to nitro olefins [13j][13k].

Scheme 7. *Possible Metathesis-Like Mechanism of the Cross-Exchange between a* Knoevenagel-*Type Substrate* (C=C) *and an Imine* (C=N)



3. Conclusions. – We have explored dynamic C=C bond processes leading to C=C/C=C cross-exchange between *Knoevenagel* condensation products by a mechanism involving formation, hydrolysis, exchange, and recondensation steps. These reactions are reversible, under thermodynamic control, and they can occur even in the absence of a basic catalyst. The secondary amine L-proline is an efficient catalyst to accelerate the formation and hydrolysis of *Knoevenagel* compounds, increasing the rate of the exchange with aldehydes or malononitriles. Moreover, L-proline is able to accelerate the rate of cross-*Knoevenagel* C=C/C=C exchange, and *Michael*-type adducts are formed during the cross-exchange process. The %-composition of products at equilibrium depended on the electron affinity of the starting substrates. Remarkably, the C=C/C=N exchange between imines and *Knoevenagel* derivatives of 1,3-dimethylbabituric acid was found to be fast and reversible in $CDCl_3$ solution at room temperature in the absence of catalyst. This feature provides access to efficient diversity generation *via* C=C/C=N exchange. It may also signify a change in mechanism to a metathesis-like process, *via* an azetidine intermediate. The results described herein enable the creation of DCLs of higher chemical diversity, thus allowing for the generation by DCC of receptors, dynamic polymers, or biomaterials of increased complexity.

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Experimental Part

General. Reagents. Thiophene-2-carbaldehyde (98%), benzaldehyde (98%), 4-(dimethylamino)-benzaldehyde (99%), $PhCH_2NH_2$ (99%), 4-nitrobenzaldehyde (98%), barbituric acid (99%), 1,3-dimethylbarbituric acid (99%), and malononitrile (99%) were purchased from *Sigma-Aldrich*. 4-Methoxybenzaldehyde (98%) was purchased from *Alfa Aesar*. 4-Chlorobenzaldehyde (98%) and L-proline (99%) were purchased from *Avocado* and *Lancaster*, and used as received. Deuterated solvents were purchased from *Euriso-Top* and used without further purification except $CDCl_3$, which was passed through a column of activated alumina (aluminium oxide *90* active basic). NMR Spectra: *Bruker Avance 400* spectrometer; referenced to the solvent; in ppm, *J* in Hz. High-resolution (HR) MS: *Bruker Micro TOF* mass spectrometer; in *m*/*z* (rel. %).

General Procedure for the Synthesis of Imines (*cf.* [17]). Equimolar amounts of amine and aldehyde were dissolved in dry CH_2Cl_2, and $MgSO_4$ was added. The mixture was stirred at r.t. overnight, and the solid was filtered off. After drying under vacuum, the products were isolated as colored oils or needles.

General Procedure for the Synthesis of the Knoevenagel *Condensation Products* (*cf.* [17]). To 30 ml of anh. EtOH were added barbituric acid or 1,3-dimethylbarbituric acid (3.0 mmol), the corresponding substituted benzaldehydes (3.0 mmol), and L-proline in a cat. amount (10%). The soln. was refluxed for 3–4 h. The *Knoevenagel* condensation products that precipitated out of the cooled soln. were filtered and washed with Et_2O, and then dried under vacuum for at least 2 h.

General Procedure for Knoevenagel *Formation and Aldehyde Exchange Reactions.* Stock solns. (60 mM; 0.5 ml) of corresponding aldehyde, and barbituric acid or malononitrile (for the formation studies) or *Knoevenagel* compounds (for the exchange reaction) were freshly prepared in (D_6)DMSO/D_2O 99:1. For the uncatalyzed reaction, 128 µl of each soln. were added to a NMR tube, followed by 344 µl of (D_6)DMSO/D_2O 99:1 to adjust to a final volume of 600 µl. For the catalyzed reaction, 38 µl of a L-proline stock soln. (12.8 mM in (D_6)DMSO/D_2O 99:1) was added to a NMR tube, followed by the addition of 128 µl of each soln. and 306 µl of (D_6)DMSO/D_2O 99:1.

Thermodynamic and Kinetics Features of Knoevenagel *Compound Formation and Aldehyde Exchange.* The half-lives ($t_{1/2}$) of the reactions were determined by the integration of the *Knoevenagel* compound C=C*H* and the aldehyde C*H*O ^{1}H-NMR signals as a function of time and analyzing the curved obtained. The equilibrium constants are obtained from the amounts of reactants and products according to *Eqn. 1*:

$$K = [\mathbf{2}]/[\mathbf{1}][\mathbf{B}] \text{ or } K = [\mathbf{3}]/[\mathbf{1}][\mathbf{M}] \quad (1)$$

The *Gibbs* free energy was calculated according to *Eqn. 2*:

$$\Delta G = -RT \ln K_{eq} \text{ [kJ mol}^{-1}\text{]} \quad (2)$$

General Procedure for Knoevenagel *C=C/C=C Cross-Exchange Reaction.* All reactions with two *Knoevenagel* compounds were carried out at 60° with a final concentration 12.8 mM and a total volume of 600 µl. Stock solns. of *Knoevenagel* compounds in (D_6)DMSO were prepared. The stock solns. of reactants were 60 mM and had a total volume of 0.5 ml. The stock soln. of L-proline was 12.8 mM and had a total volume of 0.5 ml. For the uncatalyzed reaction, 128 µl of the soln. of each *Knoevenagel* compound was added to a NMR tube, followed by 344 µl of (D_6)DMSO to adjust to a final volume of 600 µl. For the catalyzed reaction, 38 µl of a L-proline stock soln. (12.8 mM in (D_6)DMSO) was added to a NMR tube, followed by the addition of 128 µl of soln. of each *Knoevenagel* compound and 306 µl of (D_6)DMSO.

General Procedure for C=C/C=N Exchange. Stock solns. (40 mM, 0.4 ml) of *Knoevenagel* compounds were prepared in $CDCl_3$. For each reaction, 350 µl of each soln. was added to a NMR tube to obtain a final volume of 700 µl. The final soln. was 20 mM in each component. The %-composition of the reactions at equilibrium was determined by integration of the *Knoevenagel* compound C=C*H* and the imine N=C*H* ^{1}H-NMR signals, and the corresponding equilibrium constants *K* were calculated.

*5-[4-(Dimethylamino)benzylidene]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione* (**2a**) [17]. Yield: 0.620 g (80%). Orange solid. M.p. 259–260° ([21]: 262–263°]). ^{1}H-NMR (400 MHz, (D_6)DMSO): 3.12 (*s*, 6 H); 6.80 (*d*, *J* = 9.3, 2 H); 8.15 (*s*, 1 H); 8.43 (*d*, *J* = 9.3, 2 H); 10.92 (*s*, 1 H); 11.05 (*s*, 1 H).

*5-Benzylidenepyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione* (**2b**) [21]. Yield: 0.261 g (40%). White solid. ^{1}H-NMR (400 MHz, (D_6)DMSO): 7.45–7.56 (*m*, 3 H); 8.08 (*d*, *J* = 7.6, 2 H); 8.28 (*s*, 1 H), 11.23 (*s*, 1 H); 11.39 (*s*, 1 H).

*5-(4-Nitrobenzylidene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione* (**2c**) [21]. Yield: 0.72 g (92%). Pale-yellow solid. ^{1}H-NMR (400 MHz, (D_6)DMSO): 8.02 (*d*, *J* = 8.8, 2 H); 8.25 (*d*, *J* = 9.0, 2 H); 8.33 (*s*, 1 H); 11.32 (*s*, 1 H); 11.49 (*s*, 1 H).

*5-(4-Methoxybenzylidene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione* (**2d**) [17]. Yield: 0.622 g (90%). Yellow solid. ^{1}H-NMR (400 MHz, (D_6)DMSO): 3.88 (*s*, 3 H); 7.07 (*d*, *J* = 9.1, 2 H); 8.25 (*s*, 1 H); 8.37 (*d*, *J* = 8.9, 2 H); 11.17 (*s*, 1 H); 11.29 (*s*, 1 H).

*5-[4-(Thiophen-2-yl)benzylidene]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione* (**2e**) [17]. Yield: 0.580 g (87%). Brown-yellow solid. M.p. 275° ([21]: 270–271°]). ^{1}H-NMR (400 MHz, (D_6)DMSO): 7.36 (*d*, *J* = 5.0, 1 H); 8.18 (*d*, *J* = 3.9, 1 H); 8.28 (*d*, *J* = 4.6, 1 H); 8.57 (*s*, 1 H); 11.26 (*s*, 1 H); 11.30 (*s*, 1 H).

2-[4-(Dimethylamino)benzylidene]propanedinitrile (**3a**) [22]. Yield: 0.410 g (70%). Orange solid. M.p. 177–181° ([22]: 180–182°]). ^{1}H-NMR (400 MHz, (D_6)DMSO): 3.10 (*s*, 6 H); 6.86 (*d*, *J* = 9.3, 2 H); 7.84 (*d*, *J* = 9.4, 1 H); 8.05 (*s*, 1 H).

2-Benzylidenepropanedinitrile (**3b**) [23][24]. Yield: 0.128 g (83%). White solids. M.p. 84–85° ([23]: 83.5–84°]). ^{1}H-NMR (400 MHz, (D_6)DMSO): 7.61–7.72 (*m*, 3 H); 7.96 (*d*, *J* = 7.8, 2 H); 8.56 (*s*, 1 H).

2-(4-Nitrobenzylidene)propanedinitrile (**3c**) [24][25]. Yield: 0.49 g (82%). Yellow solid. M.p. 157–158° ([25]: 159–160°]). ^{1}H-NMR (400 MHz, (D_6)DMSO): 8.13 (*d*, *J* = 9.1, 2 H); 8.44 (*d*, *J* = 8.6, 2 H); 8.73 (*s*, 1 H).

2-(4-Methoxybenzylidene)propanedinitrile (**3d**) [26]. Yield: 0.45 g (80%). Pale-yellow solid. ^{1}H-NMR (400 MHz, (D_6)DMSO): 3.89 (*s*, 3 H); 7.20 (*d*, *J* = 8.8, 2 H); 7.98 (*d*, *J* = 9.1, 2 H); 8.41 (*s*, 1 H).

2-[4-(Thiophen-2-yl)benzylidene]propanedinitrile (**3e**) [27]. Yield: 0.191 g (40%). Brown-yellow solid. ^{1}H-NMR (400 MHz, (D_6)DMSO): 7.40 (*d*, *J* = 4.1, 1 H); 7.95 (*d*, *J* = 3.6, 1 H); 8.30 (*d*, *J* = 4.3 Hz, 1 H); 8.74 (*s*, 1 H).

*5-[4-(Dimethylamino)benzylidene]-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione* (**4a**) [28][29]. Yield: 0.78 g (90%). Orange solid. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.14 (*s*, 6 H); 3.38 (*s*, 3 H); 3.39 (*s*, 3 H); 6.69 (*d*, *J* = 9.5, 2 H); 8.39 (*d*, *J* = 9.3, 2 H); 8.42 (*s*, 1 H).

*5-(4-Methoxybenzylidene)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione* (**4b**) [28]. Yield: 0.73 g (88%). Yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.38 (*s*, 3 H); 3.39 (*s*, 3 H), 3.89 (*s*, 3 H); 6.96 (*d*, *J* = 9.0, 2 H); 8.30 (*d*, *J* = 8.6, 2 H); 8.50 (*s*, 1 H).

*5-Benzylidene-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione* (**4c**) [28]. Yield: 0.398 g (54%). Yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.36 (*s*, 3 H); 3.41 (*s*, 3 H); 7.43–7.53 (*m*, 3 H); 8.04 (*d*, *J* = 7.7, 2 H); 8.57 (*s*, 1 H).

*5-(4-Chlorobenzylidene)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione* (**4d**) [30]. Yield: 0.373 g (45%). Yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.36 (*s*, 3 H); 3.41 (*s*, 3 H); 7.42 (*d*, *J* = 8.6, 2 H); 8.01 (*d*, *J* = 8.9, 2 H); 8.48 (s, 1 H).

*1,3-Dimethyl-5-[4-(thiophen-2-yl)benzylidene]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione* (**4e**) [31]. Yield: 0.65 g (87%). Brown-yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.40 (*s*, 3 H); 3.41 (*s*, 3 H); 7.28 (*dd*, *J* = 4.0, 1 H); 7.89 (*d*, *J* = 5.1, 1 H); 7.96 (*d*, *J* = 5.6, 1 H).

*4-[(*E*)-(Benzylimino)methyl]-*N,N*-dimethylaniline* (**5a**) [17]. Yield: 0.698 g (98%). Pale-yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.99 (*s*, Me_2N, 6 H), 4.74 (*s*, 2 H); 6.68 (*d*, J = 8.8, 2 H); 7.21 (*m*, 1 H); 7.31 (*d*, *J* = 4.4, 4 H); 7.64 (*d*, *J* = 8.7, 2 H); 8.25 (*s*, CH=N).

*(*E*)-*N*-Benzyl-1-(4-methoxyphenyl)methanimine* (**5b**) [17]. Yield: 2.308 g (93%). Pale-yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.88 (*s*, 3 H); 4.83 (*s*, 2 H); 6.96 (*d*, *J* = 9.1, 2 H); 7.31–7.26 (*m*, 1 H); 7.39–7.34 (*m*, 4 H); 7.76 (*d*, *J* = 8.4, 2 H); 8.36 (*s*, CH=N).

*(*E*)-*N*-Benzyl-1-phenylmethanimine* (**5c**) [17]. Yield: 0.463 g (79%). Yellow oil. ^{1}H-NMR (400 MHz, (D_6)DMSO): 4.78 (*s*, 2 H); 7.25–7.30 (*m*, 1 H); 7.33–7.38 (*m*, 4 H); 7.45–7.49 (*m*, 3 H); 7.78–7.81 (*m*, 2 H); 8.52 (*s*, CH=N).

*(*E*)-*N*-Benzyl-1-(4-chlorophenyl)methanimine* (**5d**) [17]. Yield: 0.592 mg (86%). Yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.80 (*s*, 2 H), 7.38–7.25 (*m*, 7 H), 7.70 (*d*, *J* = 8.4, 2 H), 8.34 (*s*, CH=N).

*(*E*)-*N*-Benzyl-1-[4-(2-thienyl)phenyl]methanimine* (**5e**) [17]. Yield: 1.93 g (90%). Yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.80 (*s*, 2 H), 7.15–6.96 (*m*, 1 H), 7.39–7.23 (*m*, 6 H), 7.41 (*d*, *J* = 5.0, 1 H), 8.46 (*s*, CH=N).

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