A Novel Concept for Combinatorial Chemistry in Solution: Synthesis of Highly Substituted Pyrrolidines by Multicomponent Domino Reactions

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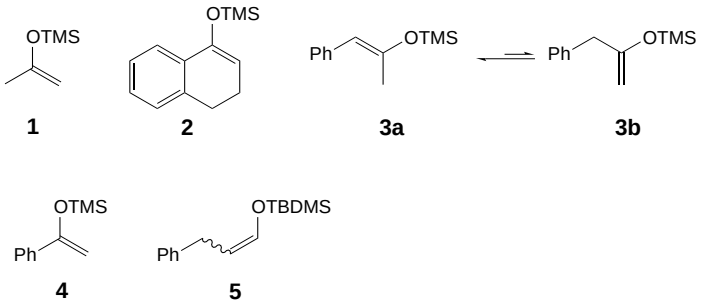
Dedicated to Professor *Dieter Seebach* on the occasion of his 65th birthday

The multicomponent domino *Knoevenagel* hetero-*Diels–Alder* hydrogenation process of *N*-[(benzyloxy)carbonyl(Cbz)-protected amino aldehydes with *N*,*N*-dimethylbarbituric acid and the trimethylsilyl enol ethers **1**–**3** leads to the formation of the substituted pyrrolidines **12**–**15**. Under the same conditions, reaction of the trimethylsilyl enol ether **4**, obtained from acetophenone, gave the primary amines **18a**,**b** probably due to a hydrogenolytic cleavage of the intermediately formed pyrrolidines. The zwitterionic products were obtained in high purity simply by precipitation with Et_2O.

Introduction. – Combinatorial chemistry is a major tool for finding and improving lead structures for medicinal applications or for the design of catalysts and new materials [1–7]. At the beginning, much effort was expended on the development of solid-phase chemistry; however, many research groups have now moved – at least in part – towards solution-phase combinatorial chemistry, which has the advantage that all known potential transformations can be tried, and binding to and cleavage from solid support is not necessary. Solution-phase chemistry usually does not allow the use of excess reagents to drive the transformations to completion, depending rather on purification of the final products by chromatography, and, thus, automation is more difficult. We have recently shown that one can combine the advantages of solid- and solution-phase chemistry by preparing zwitterions as products that are soluble in many solvents but can be precipitated in high purity by adding Et_2O to the solution [8]. In addition, for the formation of these products, we designed a new multicomponent domino process that allows the preparation of highly diversified products starting from simple substrates. Thus, the domino *Knoevenagel* [9] hetero-*Diels–Alder* [10][11] reaction of *N*-[(benzyloxy)carbonyl](Cbz)-protected α-, β-, or γ-aminoaldehydes with a 1,3-dicarbonyl compound in the presence of a benzyl enol ether followed by hydrogenation leads to the formation of substituted pyrrolidines, piperidines, and azepanes in $>95\%$ purity in most cases. A disadvantage of the described method is the necessity to use preformed benzyl enol ethers, which are usually not commercially available; in addition, it is not a simple task to obtain the benzyl enol ethers with defined configuration, also fully substituted N-heterocycles could not be prepared due to unavailability of benzyl enol ethers of ketones. We now developed a new procedure that enables us to use simple trimethylsilyl (TMS) enol ethers in the process, which are easily accessible from aldehydes and also ketones in an (*E*)- or (*Z*)-selective way [12].



Results and Discussion. – Reaction of TMS enol ether **1** with *N*,*N*′-dimethylbarbituric acid (**6**) and the protected amino aldehyde **7a** [13] in the presence of trimethyl orthoformate (TMOF) and catalytic amounts of ethylenediammonium diacetate (EDDA) in an ultrasonic bath at 50–60° for 15 h followed by hydrogenation with Pd on charcoal at 25° led to the pyrrolidine **12a**, which, due to its zwitterionic structure, could then be precipitated from MeOH by adding Et_2O in 98% purity according to HPLC.

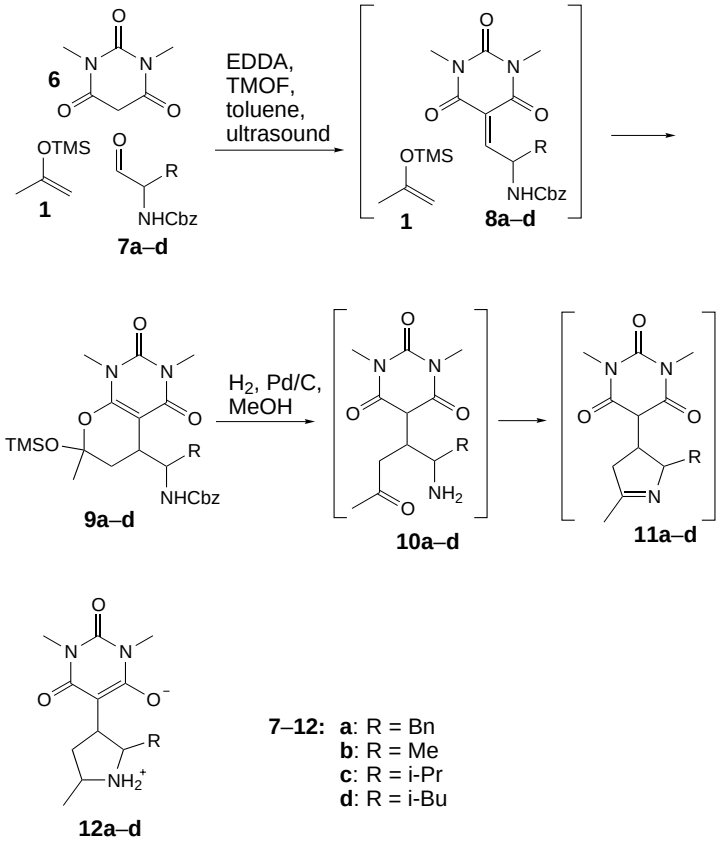
In this process, first *N*,*N*′-dimethylbarbituric acid (**6**) reacts with the amino aldehyde **7** in a *Knoevenagel* condensation to give the substituted barbituric acid **8** (*Scheme 1*), which is highly activated due to the presence of the electron withdrawing group, which lowers the energy of the LUMO. It can, therefore, react with the TMS enol ether **1** at 50–60° to provide the cycloadduct **9** in a hetero *Diels–Alder* reaction with inverse electron demand [14][15]. The addition of the orthoformate is necessary to remove H_2O formed in the *Knoevenagel* condensation; otherwise, the TMS enol ether might be cleaved, which would prevent the cycloaddition reaction.

For the formation of the pyrrolidines **12**, it was necessary to remove the Cbz protecting group from the amino moiety. This was achieved by hydrogenolysis with Pd on charcoal in MeOH. Thus, the resulting solution of crude cycloadduct **9** in toluene was evaporated and the hydrogenation performed after taking the residue up in MeOH. Under these conditions, the mixed TMS acetal moiety of **9** was also cleaved to give the ketone **10**, which reacted with the primary amine. The imine **11** formed was hydrogenated under the reaction conditions to yield the desired pyrrolidine **12** in excellent purity after precipitation with Et_2O. We also used the TBDMS enol ether **5** in the process; however, this did not lead to the desired pyrrolidine, since the cycloadduct formed first was too stable to be cleaved under the reaction conditions.

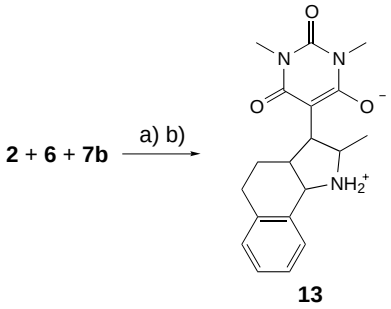
To determine the scope and limitations of the described method, we used different amino aldehydes **7a–d** and TMS enol ethers **1–4**, which were prepared according to known procedures [12]. In the reaction of amino aldehydes **7a–d** with **1** and **6**, the desired pyrrolidines were obtained in 91–98% purity. Similarly, the domino *Knoevenagel* hetero-*Diels–Alder* hydrogenation process of the amino aldehyde **7b** with **6** and the TMS enol ether **2** led to formation of the heterocycle **13** in >95% purity (*Scheme 2*).

In the reaction of the amino aldehyde **7b** with **6** and the TMS enol ether **3**, a 1:1.1 mixture of the pyrrolidines **14** and **15** was obtained (*Scheme 3*). This primarily unexpected result can be explained by assuming that, under the reaction conditions, **3a** partly isomerizes to **3b**, which should undergo the hetero-*Diels–Alder* reaction at a

Scheme 1



Scheme 2

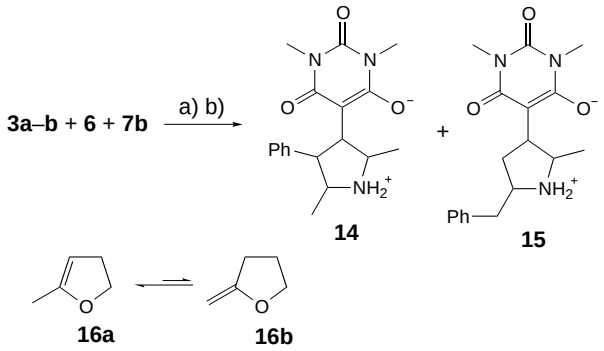


a) EDDA, TMOF, toluene, ultrasound. b) H_2, Pd/C, MeOH.

higher rate due to the lower steric hindrance in the transition state. A similar effect has been observed by us in the hetero-*Diels–Alder* reaction of 5-methyl-2,3-dihydrofuran (**16a**), where, at ambient pressure, mainly a spiro compound was obtained from the

intermediate formed, 2-methylidenetetrahydrofuran **16b**. Under high pressure, a shift to the annulated cycloadduct took place [16].

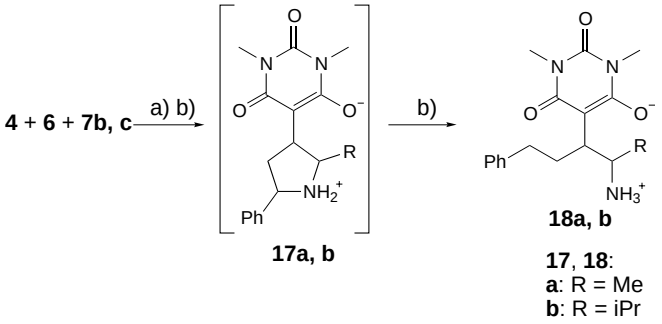
Scheme 3



a) EDDA, TMOF, toluene, ultrasound. b) H_2, Pd/C, MeOH.

Finally, we also checked the use of the TMS enol ether **4**, obtained from acetophenone. In these reactions, not the desired pyrrolidines but substituted primary amines **18a**,**b**, which may also be of interest, were obtained (*Scheme 4*). We assume that the transformations take place as usual; however, the pyrrolidinium-pyrimidinolates (**17a**,**b**) obtained are not stable under the reaction conditions but undergo hydrogenolysis to give the final products.

Scheme 4



a) EDDA, TMOF, toluene, ultrasound. b) H_2, Pd/C, MeOH.

In all reactions, several new stereogenic centers are formed; thus, in the case of **12**, four diastereoisoisomers and, in the case of **13**, even eight diastereoisomers may be expected. In contrast, in the domino process of **1**, **6**, and **7a**, as well as **1**, **6**, and **7c**, only single diastereoisomers **12a** and **12c** ($> 95:1$), respectively, were found, and, in the transformations of **1**, **6**, and **7b**, as well as **2**, **6**, and **7b**, two diastereoisoisomers were obtained in ratios of 2 : 1 and 1.5 : 1, respectively; these, however, could not be separated. The unexpectedly high stereoselectivity is probably due to induction of pronounced

facial selectivity in the hetero-*Diels–Alder* reaction, which can be the result of the rigid transition structure due to 1,3-allylic strain [17][18].

Conclusions. – We have shown that the multicomponent domino *Knoevenagel* hetero-*Diels–Alder* hydrogenation reaction process of Cbz-protected amino aldehydes with a 1,3-dicarbonyl compound as *N,N′*-dimethylbarbituric acid and TMS enol ethers is a powerful and efficient method for the synthesis of highly substituted pyrrolidines. It combines the advantages of solution- and solid-phase syntheses for combinatorial chemistry, since excess reagents can be used, and purification is possible by simple precipitation.

Experimental Part

General. ^{1}H-NMR and ^{13}C-NMR Spectra: *Varian Inova-500* or *Bruker AMX-300*; δ in ppm, J in Hz. MS: *Finnigan MAT-95*; *m/z* (%). HPLC: *Cram Superspher 100 R18* (100 mm × 2 mm).

General Procedure (GP) *for the Domino Reaction Sequence:* The Cbz-protected aminoaldehydes **7** (1.0 equiv.), *N,N′*-dimethylbarbituric acid (**6**; 1.0 equiv.) and TMS enol ethers **1**–**5** (4.0 equiv.) were allowed to react in toluene (4 ml/mmol) and trimethyl orthoformate (0.8 ml/mmol) with a few crystals of EDDA under Ar in a 10 ml pressure flask in an ultrasonic bath for 15 h at 50–60°. After removal of the solvent *in vacuo*, the residue was dissolved in MeOH (4 ml/mmol) and stirred under H_2 with Pd on charcoal (10%, 0.10 g/mmol) for 24 h. Subsequently, the catalyst was removed by filtration through a small amount of *Celite*, washed with MeOH, and the solvent removed *in vacuo*. The residue was dissolved in a small amount of MeOH, and the product precipitated by the addition of Et_2O. The white, amorphous precipitate was filtered off and washed with Et_2O. The purity of the products was measured by HPLC.

5-(2-Benzyl-5-methylpyrrolidin-1-ium-3-yl)-1,3-dihydro-1,3-dimethyl-2,6-dioxopyrimidin-4-olate (**12a**). Reaction of O-*benzyl*-N-*(1-oxo-3-phenylprop-2-yl)carbamic acid* (**7a**; 35.4 mg, 125 μmol), N,N′-*dimethylbarbituric acid* (**6**; 19.5 mg, 125 μmol), and trimethyl(propen-2-yloxy)silane (**1**; 130 mg, 1.00 mmol) according to the *GP* gave 14 mg (34%) of **12a** (98% pure; diastereoisomer ratio > 95 : 1). ^{1}H-NMR ((D$_6$)DMSO, 500 MHz): 1.29 (*d*, *J* = 6.5, Me–C(5′)); 1.91, 1.93 (2*t*, *J* = 9.8, H_2C(4′)); 2.79–2.83 (*m*, CH_2Ph); 3.04 (*s*, 2 MeN); 3.43–3.51, 3.62–3.70 (2*m*, H–C(2′), H–C(5′)); 4.15–4.21 (*m*, H–C(3′)); 7.16–7.29 (*m*, 5 arom. H). ^{13}C-NMR ((D$_6$)DMSO, 75 MHz): 18.07 (*Me*–C(5′)); 26.80 (MeN); 35.83, 36.74 (C(4′), *C*H$_2$Ph); 40.21, 53.82, 61.43 (C(2′), C(3′), C(5′)); 82.06 (C(5)); 126.3, 128.3, 128.7, 137.7 (arom. C); 152.6 (C(2)); 162.1 (C(4), C(6)). EI-MS (70 eV): 329.3 (3, M^+), 238.2 (100, $[M - Bn]^+$). HR-MS: 329.1739 ($C_{18}H_{23}N_3O_3$; calc. 329.1739).

5-(2,5-Dimethylpyrrolidin-1-ium-3-yl)-1,3-dihydro-1,3-dimethyl-2,6-dioxopyrimidine-4-olate (**12b**). Reaction of O-*benzyl*-N-*(1-oxoprop-2-yl)carbamic acid* (**7b**; 25.9 mg, 125 μmol), **6** (19.5 mg, 125 μmol), and **1** (130 mg, 1.00 mmol) according to the *GP* gave 17 mg (54%) of **12b** (94% pure; diastereoisomer ratio 2 : 1). ^{1}H-NMR ((D$_6$)DMSO, 500 MHz): 0.99, 1.11 (2*d*, *J* = 6.5, Me–C(2′)); 1.30, 1.32 (2*d*, *J* = 6.0, Me–C(5′)); 1.85–1.91, 2.00–2.07 (2*m*, H_2C(4′)); 3.02, 3.08 (2*s*, 2 MeN); 3.30–3.70 (*m*, H–C(2′), H–C(5′)); 3.84–3.91 (*m*, H–C(3′)). EI-MS (70 eV): 253.2 (2, M^+), 238.2 (12, $[M - Me]^+$), 97.1 (100, $[M - C_6H_8N_2O_3]^+$), 82.1 (48, $[M - C_6H_8N_2O_3 - Me]^+$). HR-MS: 253.1426 ($C_{12}H_{19}N_3O_3$; calc. 253.1426).

1,3-Dihydro-5-(2-isopropyl-5-methylpyrrolidin-1-ium-3-yl)-1,3-dimethyl-2,6-dioxopyrimidin-4-olate (**12c**). Reaction of O-*benzyl*-N-*(3-methyl-1-oxobutan-2-yl)carbamic acid* (**7c**; 29.4 mg, 125 μmol), **6** (19.5 mg, 125 μmol), and **1** (130 mg, 1.00 mmol) according to the *GP* gave 29 mg (83%) of **12c** (93% pure; diastereoisomer ratio > 95 : 1). ^{1}H-NMR ((D$_6$)DMSO, 500 MHz): 0.88, 0.91 (2*d*, *J* = 6.5, *Me*$_2$CH); 1.31 (*d*, *J* = 6.5, Me–C(5′)); 1.74 (*oct*, *J* = 6.5, Me$_2$C*H*); 1.88–2.02 (*m*, H_2C(4′)); 3.02 (*s*, 2 MeN); 3.44–3.51 (*m*, H–C(2′), H–C(5′)); 3.67–3.74 (*m*, H–C(3′)). ^{13}C-NMR ((D$_6$)DMSO, 125 MHz): 17.63, 18.88, 18.99 (*Me*$_2$CH, *Me*–C(5′)); 26.92, 29.51 (Me$_2$*C*H, MeN); 36.44, 37.93 (C(3′), C(4′)); 54.41, 66.07 (C(2′), C(5′)); 83.31 (C(5)); 152.8 (C(2)); 161.9 (C(4), C(6)). EI-MS (70 eV): 281.2 (5, M^+), 238.1 (100, $[M - i\text{-}Pr]^+$). HR-MS: 281.1739 ($C_{14}H_{23}N_3O_3$; calc. 281.1739).

1,3-Dihydro-1,3-dimethyl-5-[5-methyl-2-(2-methylpropyl)pyrrolidin-1-ium-3-yl]-2,6-dioxopyrimidin-4-olate (**12d**). Reaction of O-*benzyl*-N-*(4-methyl-1-oxopentan-2-yl)carbamic acid* (**7d**; 31.2 mg, 125 μmol), **6** (19.5 mg, 125 μmol), and **1** (130 mg, 1.00 mmol) according to the *GP* gave 17 mg (46%) of **12d** (91% pure). EI-MS (70 eV): 295.2 (11, M^+), 238.1 (100, $[M - C_4H_9]^+$), 139.1 (30, $[M - C_6H_8N_2O_3]^+$). HR-MS: 295.1895 ($C_{15}H_{25}N_3O_3$; calc. 295.1896).

*5-(2,3,3a,4,5,9b-Hexahydro-2-methyl-1*H*-benzo[g]indol-1-ium-3-yl)-1,3-dihydro-1,3-dimethyl-2,6-dioxopyrimidin-4-olate* (**13**). Reaction of **7b** (51.8 mg, 0.250 mol), **6** (39.0 mg, 0.250 mmol), and (3,4-dihydronaphthalen-1-yloxy)trimethyl silane (**2**, 206 mg, 1.00 mmol) according to the *GP* gave 18 mg (42%) of **13** (> 95%

pure; diastereoisomer ratio 1.5:1). ^{1}H-NMR ((D$_6$)DMSO, 300 MHz): 1.01, 1.16 (2*d*, *J* = 6.5, Me–C(2′)); 1.45–1.70 (*m*, H$_2$C(4′)); 2.57–3.25 (*m*, H–C(3′), H$_2$C(5′), 2 MeN); 3.38–3.75 (*m*, H–C(3a′)); 4.02–4.12 (2*d*, ^3J = 6.5, H–C(2′)); 4.42, 4.58 (2*d*, ^3J = 10.0, H–C(9b′)); 7.10–7.58 (*m*, 4 arom. H). DCI-MS (200 eV): 342.2 (100, $[M+1]^+$), 359.3 (14, $[M+18]^+$); consistent with $C_{19}H_{23}N_3O_3$ (341.2).

1,3-Dihydro-1,3-dimethyl-5-(2,5-dimethyl-4-phenylpyrrolidin-1-ium-3-yl)-2,6-dioxopyrimidin-4-olate (**14**) *and 5-(5-Benzyl-5-methylpyrrolidin-1-ium-3-yl)-1,3-dihydro-1,3-dimethyl-2,6-dioxopyrimidin-4-olate* (**15**). Reaction of **7b** (25.9 mg, 125 μmol), **6** (19.5 mg, 125 μmol), and trimethyl(1-phenylpropen-2-yloxy)silane (**3a**; 0.46 g, 33% in phenylacetone, 1.0 mmol) according to the *GP* gave 20 mg (47%) of **14** and **15** in a ratio of 1:1.1 (98% pure). EI-MS (70 eV): mixture: 320 (2, M^+), 238 (100, $[M-Bn]^+$), 82 (72, $[C_5H_8N]^+$). HR-MS: 329.1739 ($C_{18}H_{23}N_3O_3$; calc. 329.1739).

Data of **15**: ^{1}H-NMR ((D$_6$)DMSO/D$_2$O, 500 MHz): 1.09 (*d*, *J* = 6.5, Me–C(2′)); 1.83–1.87, 1.94–2.62 (2*m*, 2 H–C(4′)); 2.89–3.06 (*m*, 2 MeN, C*H*$_2$Ph); 3.12–3.19 (*m*, H–C(3′)); 3.76–3.83 (*m*, H–C(5′)); 3.89–3.98 (*m*, H–C(2′)); 7.17–7.24 (*m*, 5 arom. H). ^{13}C-NMR (D$_6$)DMSO/D$_2$O, 125 MHz): 17.25 (*Me*–C(2′)); 28.67 (MeN); 34.66 (C(4′), *C*H$_2$Ph); 42.40 (C(3′)); 57.55, 59.98 (C(2′), C(5′)); 85.65 (C(5)); 128.3, 130.1, 130.2, 137.8 (arom. C); 154.5 (C(2)); 164.6 (C(4), C(6)).

Data of **14**: ^{1}H-NMR ((D$_6$)DMSO/D$_2$O, 500 MHz): 1.20 (2*d*, *J* = 6.5, Me–C(2′), Me–C(5′)); 2.95 (*s*, 2 MeN); 3.45–3.52 (*m*, H–C(3′), H–C(5′)); 3.67–3.74 (*m*, H–C(4′)); 3.89–3.98 (*m*, H–C(2′)); 7.17–7.24 (*m*, arom. H).

1,3-Dihydro-1,3-dimethyl-5-(1-methyl-4-phenylbutylammonium-2-yl)-2,6-dioxopyrimidin-4-olate (**18a**). Reaction of **7b** (25.9 mg, 125 μmol), **6** (19.5 mg, 125 μmol), and trimethyl (3-phenylpropen-2-yloxy)silane (**4**; 0.20 g, 1.0 mmol) according to the *GP* gave 16 mg (40%) of **18a** (> 95% pure). ESI-MS: 340.4 (45, $[M+Na]^+$), 657.1 (100, $[2M+Na]^+$); consistent with $C_{17}H_{23}N_3O_3$ (317.1).

1,3-Dihydro-5-(1-isopropyl-4-phenylbutylammonium-2-yl)-1,3-dimethyl-2,6-dioxopyrimidin-4-olate (**18b**). Reaction of **7c** (29.4 mg, 125 μmol), **6** (19.5 mg, 125 μmol), and **4** (0.20 g, 1.0 mmol) according to the *GP* gave 24 mg (56%) of **18b** (95% pure). MS (ESI): 368.5 (45, $[M+Na]^+$), 713.1 (100, $[2M+Na]^+$); consistent with $C_{19}H_{27}N_3O_3$ (345.2).

This work was supported as part of the *Bundesministerium für Bildung und Forschung* Project 'Kombinatorische Chemie' (grant number 03D00562). We thank *BASF AG* (D-Ludwigshafen) and the *Fonds der Chemischen Industrie* for generous support.

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Received August 3, 2002