The Flögel-three-component reaction with dicarboxylic acids – an approach to bis(β-alkoxy-β-ketoenamides) for the synthesis of complex pyridine and pyrimidine derivatives

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Abstract
An extension of the substrate scope of the Flögel-three-component reaction of lithiated alkoxyallenes, nitriles and carboxylic acids is presented. The use of dicarboxylic acids allowed the preparation of symmetrical bis(β-ketoenamides) from simple starting materials in moderate yields. Cyclocondensations of these enamides to 4-hydroxypyridine derivatives or to functionalized pyrimidines efficiently provided symmetrically and unsymmetrically substituted fairly complex (hetero)aromatic compounds containing up to six conjugated aryl and hetaryl groups. In addition, subsequent functionalizations of the obtained heterocycles by palladium-catalyzed couplings or by oxidations are reported. We also describe the simple synthesis of a structurally interesting macrocyclic bispyrimidine derivative incorporating a 17-membered ring, whose configuration was elucidated by DFT calculations and by subsequent reactions.

Introduction
Multicomponent reactions (MCRs) generally allow a diversity-oriented fast and efficient access to complex synthetic intermediates and are thus powerful tools for the assembly of small-molecule libraries [1,2]. MCRs leading to functionalized N-heterocycles [3-7] have long been known before the general concept of MCRs was introduced, e.g. the Hantzsch dihydro-
permanent high interest. In the course of exploring the reactivity of alkoxyallenes and their utilization as C-3 building blocks [34-37] our group developed a highly flexible method to synthesize \(\beta\)-alkoxy-\(\beta\)-ketoenamides of type 1 that are remarkably versatile cyclization precursors for the synthesis of functionalized heterocycles such as 4-hydroxypyridines [38-44], furopyridines [45], 5-acetyloxazoles [46,47], pyrimidines [43,48,49] and their corresponding N-oxides [50] (Scheme 1).

This approach – discovered and mechanistically elucidated by Oliver Flögel – features a three-component reaction that employs alkoxyallenes, nitriles and carboxylic acids: upon treatment with \(n\)-butyllithium the allene is lithiated in \(\alpha\)-position to the alkoxy moiety; the addition of a nitrile as electrophile to this highly reactive nucleophile results in the formation of an iminoallene adduct [38] that is protonated and subsequently acylated by the addition of a carboxylic acid furnishing a \(\beta\)-alkoxy-\(\beta\)-ketoenamide 1. A detailed mechanistic proposal for this reaction has been disclosed in previous reports [38,39].

Our earlier investigations revealed that this method tolerates a broad variety of differently substituted starting materials – inter alia (het-)aromatic and (branched) aliphatic nitriles and carboxylic acids. It is also noteworthy to mention that the configurational integrity of enantiopure \(\alpha\)-chiral carboxylic acids and/or nitriles is retained during this reaction [40]. In the present report we describe our efforts to further broaden the substrate scope of this multicomponent reaction and the subsequent cyclizations by employing aromatic dicarboxylic acids. This extension should allow a rapid access to fairly complex heteroaromatic systems containing up to six conjugated aryl and hetaryl groups. Complementary examples employing aromatic dinitriles in this Flögel-three-component reaction have previously been presented [39].

Results and Discussion

As typical model substrates we chose to employ isophthalic acid (11) and diphenic acid (12) in combination with methoxyallene (7), pivalonitrile (9) and thiophene-2-carbonyl nitrile (10) in the three-component reaction (Scheme 2). Gratifyingly we were able to isolate the expected bis(\(\beta\)-ketoenamides) 13–15 in reasonable yields of 15–28%. Taking the number of individual steps into account (six new bonds are formed for

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**Scheme 1:** Flögel-three-component reaction of lithiated alkoxyallenes, nitriles and carboxylic acids providing \(\beta\)-alkoxy-\(\beta\)-ketoenamides 1 – versatile precursors for the synthesis of functionalized \(N\)-heteroaromatics 2–6.
Scheme 2: Synthesis of bis(\(\beta\)-ketoenamides) 13–15 by three-component reactions of lithiated methoxyallen 8 with nitriles 9 or 10 and isophthalic acid (11) or diphenic acid (12).

After these successful multicomponent reactions we investigated the intramolecular condensations of the bis(\(\beta\)-ketoenamides) 13–15 to pyridine and pyrimidine derivatives. Enamides 13 and 14 were treated with trimethylsilyl trifluoromethanesulfonate (TMSOTf) and triethylamine to provide the bis(4-hydroxyypyridines) 16 in 50% yield and 18a in 60% yield, respectively (Scheme 3). A mechanistic proposal for this aldol type condensation has been presented in a previous report [53]. For precursor 14 partial monocyclization was observed under the applied conditions, affording in 18% yield 4-hydroxyypyridine 18b with a retained \(\beta\)-ketoenamide moiety. Treatment of compounds 16, 18a and 18b with sodium hydride followed by nonfluorobutanesulfonyl fluoride (N\(\text{F}\)) provided the corresponding sulfonates 17, 19 and 20 in yields in the range of 60–72%. Pyrid-4-yl nonaflates are excellent precursors for transition metal-catalyzed cross-coupling reactions [42,54-58], which was demonstrated here by the successful Suzuki coupling of bisononaflate 19 with (\(E\))-styrylboronic acid and the Stille coupling of 19 with 2-(tributylstannyl)thiophene. Albeit the expected twofold coupling products 21 and 22 were obtained in only moderate yields, the presented approach nevertheless features a quite rapid access to these fairly complex heteroaromatic systems containing six conjugated aryl and hetaryl groups. Upon excitation with UV light (253 nm) compound 22 shows fluorescence with a maximum intensity at 378 nm (see Supporting Information File 1 for details). The photophysical properties of structurally related pyridine–thiophene conjugates were recently investigated in detail [55,57,58].

Next, we investigated the cyclocondensation of bis(\(\beta\)-ketoenamides) 13–15 to pyrimidines (Scheme 4) using ammonium acetate as ammonia source. Initially we subjected enamide 13 to conditions that had been optimized for mono-\(\beta\)-ketoenamides [48,49], in this case resulting in incomplete conversion: after heating 13 with 8 equiv of ammonium acetate in a sealed tube we obtained a 1:1 mixture of bis(pyrimidine) derivative 23a and...
Scheme 3: Cyclocondensations of β-ketoenamides 13 and 14 to 4-hydroxypyridines 16, 18a and 18b, their subsequent nonaflations and palladium-catalyzed coupling reactions of 19 leading to compounds 21 and 22. NFF = C₄F₉SO₂F

Although initially not desired the incomplete conversions of the bis(β-ketoenamides) leading to mono-pyridine derivatives such as 18b or to mono-pyrimidine derivatives like 23b and 24b provided new synthetic options to construct unsymmetrically substituted mixed heteroaromatic systems. As an example we used mono-pyrimidine derivative 24b and cyclized its β-ketoenamide moiety by treatment with TMSOTf and triethylamine. Pyrimidine/pyridinol derivative 26 was isolated in 79% yield (Scheme 5) and subsequently converted into the corresponding nonaflate 27 in 70% yield.

As recently described, β-alkoxy-β-ketoenamides may also be directly cyclized to pyrimidine-N-oxides under mild conditions if hydroxylamine hydrochloride is used as reagent [50]. Accordingly, the reactions of β-ketoenamides 14 and 20 with hydroxylamine hydrochloride provided the symmetric bis(pyrimidine-N-oxide) 28 in 39% yield or the mono-pyrimidine-N-oxide 30 in 54% yield (Scheme 6). The acetoxylation of 2- and 4-alkyl substituted pyridine-N-oxides by treatment with acetic anhydride is known as the Boekelheide rearrangement [59,60]. For pyrimidine-N-oxides however, only few examples of this type of transformation have been reported [50,61-65]. Therefore we were pleased to find that upon treatment with acetic anhydride the obtained pyrimidine-N-oxides 28 and 30 smoothly under-
Scheme 4: Cyclocondensations of β-ketoamides 13–15 with ammonium acetate to bis(pyrimidine) derivatives 23a, 24a and 25 and mono-pyrimidines 23b and 24b.

Scheme 5: Conversion of mono-pyrimidine derivative 24b into unsymmetrically substituted biphenylene-bridged pyrimidine/nonafloropyridine conjugate 27. NfF = C4F9SO2F

went the expected rearrangement to give the acetoxy methyl-substituted pyrimidine derivatives 29 and 31 in 61% and 55% yield, respectively. This approach thus allows the simple functionalization of the 4-methyl group of the pyrimidine derivatives and is a very useful tool for the preparation of other compounds.
Scheme 6: Condensation of \( \beta \)-ketoenamides 14 and 20 with hydroxylamine hydrochloride to pyridine-N-oxides 28 and 30 and their subsequent Boekelheide rearrangements furnishing functionalized bis(pyrimidine) derivative 29 and pyrimidine/pyridine conjugate 31.

An alternative option for the side chain functionalization of 4- or 6-methyl substituted pyrimidines involves an oxidation with selenium dioxide (Riley oxidation [66-68]). To explore the synthetic potential of the newly prepared compounds we exemplarily oxidized bis(pyrimidine) 23a by this method in order to finally prepare a macrocyclic compound such as 34 (Scheme 7). Treatment of 23a with an excess of selenium dioxide at 90 °C resulted in the formation of an inseparable mixture of two different aldehydes (probably the dialdehyde and the monoadehyde). After reduction of the mixture with sodium borohydride the obtained products could be separated by column chromatography providing the dialcohol 32a in 51% yield over two steps and the monoalcohol 32b in 25% yield, respectively. The subsequent O-allylation of 32a furnished bisallyl ether 33 with 77% yield that was subjected to a ring closing metathesis (RCM) [69] with Grubbs-II-catalyst smoothly leading to the struc-

Scheme 7: Riley oxidation of bis(pyrimidine) derivative 23a and conversion of diol 32a into macrocycle 34.
turally interesting macrocyclic compound \(34\) in 73% yield. Compounds of this type – incorporating a 17-membered ring – have the potential to serve as structurally quite unique ligands for a variety of applications, e.g. in catalysis.

With ruthenium-based catalysts bearing \(N\)-heterocyclic carbene (NHC) ligands, RCM usually delivers macrocyclic olefins as mixtures of \(E\)- and \(Z\)-isomers, in most cases in favor of the \(E\)-isomer [70-73]. The \(E/Z\)-ratio is often under thermodynamic control, reflecting the energy difference between the two isomers. According to TLC and NMR spectroscopy, macrocycle \(34\) was isolated as a single compound. Due to the symmetry of \(34\) no couplings of the olefinic protons in its \(^1\)H NMR spectrum can be observed. Thus at this stage, we were unable to assign the configuration of the double bond. In lack of suitable crystals for an X-ray analysis, we calculated the energy for the two possible isomers of \(34\), suggesting that the \(E\)-isomer should be considerably more stable than the corresponding \(Z\)-isomer (Table 1). Using the semi-empirical AM1 method an energy difference of \(\Delta E_{Z,E}\) of 28.7 kJ/mol was determined. DFT calculations using the B3LYP method with the basis sets 6-31(d) or 6-31G(d,p) both gave a \(\Delta E_{Z,E}\) value of 16.4 kJ/mol. This energy difference may be attributed to the strain of the macrocycle and higher torsion angles between the central benzene unit and the pyrimidine rings for the \(Z\)-isomer of \(34\), resulting in less efficient conjugation of the aromatic \(\pi\)-systems.

In order to unambiguously identify the double bond configuration of \(34\), we oxidized this compound with potassium osmate/NMO to obtain the vicinal diol \(35\) in 76% yield (Scheme 8). In the case of a \(Z\)-configured olefin \(34\) this dihydroxylation should give a \(\text{cis}\) configured diol (meso compound), whereas an \(E\)-configured olefin \(34\) would lead to a racemic mixture of the corresponding \(\text{trans}\) configured diol. However, due to the symmetry of both vicinal diols a distinction between \(\text{cis}\) and \(\text{trans}\) \(35\) (\(\sigma_v\) or \(C_2\)-symmetry respectively) by NMR is still not possible. The resulting diol \(35\) was therefore treated with an excess of (S)-Mosher’s acid chloride to obtain the bis-(R)-Mosher ester \(36\) [74]. TLC analysis and NMR-spectroscopy revealed, that compound \(36\) was obtained as a pair of \(C_2\)-symmetric diastereomers and that the obtained diol \(35\) was

The optimized molecular geometries of \(E\)-\(34\) and \(Z\)-\(34\) as well as the calculated torsion angles are depicted in Figure 1.

| Entry | Method          | \(\Delta E_{Z,E}\) (kJ/mol) |
|-------|-----------------|-------------------------------|
| 1     | AM1             | 28.7                          |
| 2     | B3LYP/6-31(d)   | 16.4                          |
| 3     | B3LYP/6-31G(d,p)| 16.4                          |

**Figure 1**: Optimized geometries of (a) \(E\)-configured and (b) \(Z\)-configured macrocycle \(34\) at B3LYP/6-31G(d,p) level. The numbers represent the calculated torsion angles between the aromatic rings.
in fact a racemic mixture. This observation allowed the conclusion that the RCM reaction of 33 produced the expected thermodynamically more stable E-configured macrocyclic olefin 34. Hence this experimental result is in perfect agreement with the DFT calculations.

Conclusion
We were able to extend the substrate scope of the Flögel-three-component reaction of alkoxyallenes, nitriles and carboxylic acids by successfully utilizing aromatic dicarboxylic acids to prepare three new bis(β-methoxy-β-ketoenamides). With these products of a multicomponent reaction we performed cyclizations to rapidly construct symmetrically and unsymmetrically substituted pyridine and pyrimidine derivatives. Hence a very short approach to fairly complex functionalized oligoaromatic systems was established. In addition we exemplarily investigated subsequent transformations of these compounds either by palladium-catalyzed cross-couplings or by oxidations of the 4-methyl groups of the pyrimidine subunits. Although the yields for the crucial initial multicomponent reactions leading to the bis(β-methoxy-β-ketoenamides) are only moderate when dicarboxylic acids are used the simplicity of the processes and the diversity of the products accessible is impressive. The described methods allow the preparation of oligo(hetero)aromatic compounds not available by alternative procedures.

Experimental
General methods
Reactions were performed under an atmosphere of argon in flame-dried flasks. Solvents and liquid reagents were added by syringe. Et$_2$O, CH$_2$Cl$_2$ and THF were transferred from a MB SPS-800-dry solvent system into the reaction vessels. Dry DMF was purchased from Acros Organics and stored in the presence of molecular sieve under an atmosphere of argon. NEt$_3$ was distilled from CaH$_2$ and stored over KOH under argon. Methoxyallene was prepared from propargylic alcohol in two steps according to literature procedures [34,75]. All other solvents and reagents were purchased from commercial suppliers and were used without further purification. Thin-layer chromatography (TLC) analyses were performed on TLC plates purchased from Merck (silica gel 60, fluorescence indicator F254, 0.25 mm layer thickness). Products were purified by flash column chromatography on silica gel 60 (230–400 mesh, Macherey-Nagel). NMR spectra were recorded with Bruker (AC 500, AVIII 700) and JEOL (ECX 400, Eclipse 500) instruments. Chemical shifts are reported relative to solvent residual peaks or TMS. Integrals are in accordance with assignments, and coupling constants are given in Hz. All $^{13}$C NMR signals of Nf-groups [CF$_3$(CF$_2$)$_3$] are not given since unambiguous assignment is not possible due to strong splitting by coupling with the $^{19}$F nuclei. IR spectra were measured with a Jasco FT/IR-4100 spectrometer. HRMS analyses were performed with a Varian Ionspec QFT-7 (ESI–FT ICRMS) or an Agilent 6210 (ESI–TOF) instrument. Melting points were measured with a Reichert apparatus (Thermovar) and are uncorrected.

Three-component-reaction of methoxyallene, nitriles and dicarboxylic acids (typical procedure 1)
To a solution of methoxyallene (7, 2.07 g, 29.6 mmol) in dry Et$_2$O (25 mL) was added n-BuLi (10.8 mL, 27.0 mmol, 2.5 M in hexanes) at −50 °C. After 30 min stirring at −50 °C, the reaction mixture was cooled to −78 °C and pivalonitrile (9, 0.752 g, 9.06 mmol) in dry Et$_2$O (10 mL) was added to the mixture. After stirring for 4 h a suspension of diphenic acid (12, 6.54 g, 27.0 mmol) in dry Et$_2$O (50 mL) was added. The temperature was allowed to rise to rt and the mixture was stirred overnight. The reaction was quenched with sat. aq NaHCO$_3$ solution (25 mL) and the layers were separated. The aqueous layer was extracted with Et$_2$O (3 × 50 mL) and the combined organic layers were washed with brine (25 mL), dried with Na$_2$SO$_4$ and filtered. The solvent was removed under reduced pressure and
the obtained crude product was purified by column chromatography (silica gel, hexanes/EtOAc = 1:2) to provide bis(β-ketoenamide) 14 (1.39 g, 28%) as a pale yellow solid.

\[ N^2,N^2'-\text{Bis}(4\text{-methoxy-2,2-dimethyl-5-oxohex-3-en-3-yl)biphenyl-2,2'-dicarboximide} (14): \text{mp} 140–143 \degree \text{C}; \text{IR} (\text{ATR}) \nu: 3145 (\text{NH}), 3040–2835 (=\text{C-H}, \text{C-H}), 1695 (\text{C=O}), 1550–1445 (\text{C=C}) \text{ cm}^{-1} ; \text{1}^1\text{H NMR (CDCl}_3, 500 \text{ MHz}) \delta 1.19 (s, 18H, t-Bu), 3.89 (s, 6H, OMe), 6.92 (s, 2H, Py), 7.10 (dd, \text{J} = 7.5, 1.2 \text{ HZ}, 2H, Ar), 7.30 (td, \text{J} = 7.5, 1.4 \text{ HZ}, 2H, Ar), 7.36 (dd, \text{J} = 7.5, 1.4 \text{ HZ}, 2H, Ar), 7.59 (dd, \text{J} = 7.5, 1.2 \text{ HZ}, 2H, Ar) \text{ ppm}; \text{13}^\text{C} \text{NMR (CDCl}_3, 126 \text{ MHz}) \delta 29.1, 38.7 (q, s, t-Bu), 61.7 (q, OMe), 115.2 (d, Py), 127.4, 128.6, 130.1, 131.6 (4 d, Ar), 138.2, 140.6 (2 s, Ar), 145.3, 149.3, 153.2, 163.7 (4 s, Py) \text{ ppm}; \text{19}^\text{F} \text{NMR (CDCl}_3, 470 \text{ MHz}) \delta -80.6 (t, \text{J} = 9.6 \text{ HZ}, 6F, \text{CF}_3), -109.5 (t, \text{J} = 13.7 \text{ HZ}, 4F, \text{CF}_2), -120.7, -125.8 (2 \text{ m}, 4F \text{ each, } \text{CF}_2) \text{ ppm}; \text{ESI–TOF (m/z): } [\text{M} + \text{Na}]^+ \text{ cale}d \text{ for } C_{40}H_{34}F_3N_2NaO_8S_2, 1099.1361; \text{found, } 1099.1394. \]

Cyclization of \( \beta \)-ketoenamides to pyrimidines (typical procedure 4)

Bis(\( \beta \)-ketoenamide) 14 (0.162 g, 0.296 mmol) and NH$_4$OAc (0.365 g, 4.73 mmol) were placed in an ACE-sealed tube. The mixture was dissolved in MeOH (5 mL) and stirred for 2 d at 90 °C. After addition of H$_2$O (10 mL) and Et$_2$O (20 mL) the layers were separated and the aqueous layer was extracted with Et$_2$O (2 × 25 mL). The combined organic layers were dried with Na$_2$SO$_4$, filtered and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, hexanes/EtOAc = 5:1) to provide pyrimidines 24a (88 mg, 56%), and 24b (35 mg, 23%), both as colorless oils.

2,2'-(4-tert-buty1-5-methoxy-6-methylpyrimidin-2-yl)biphenyl (24a): \text{IR} (\text{ATR}) \nu: 3070–2855 (=\text{C-H}, \text{C-H}), 1550–1440 (\text{C=C}) \text{ cm}^{-1} ; \text{1}^1\text{H NMR (CDCl}_3, 500 \text{ MHz}) \delta 0.99 (s, 18H, t-Bu), 2.31, 2.33 (2 s, 3H each, Me), 3.42, 3.70 (2 s, 3H each, OMe), 6.64 (dd, \text{J} = 7.5, 1.0 \text{ Hz}, 2H, Ar), 7.10 (dd, \text{J} = 7.7, 1.0 \text{ Hz}, 2H, Ar) \text{ ppm}; \text{13}^\text{C} \text{NMR (CDCl}_3, 126 \text{ MHz}) \delta 19.7 (q, Me), 28.7, 37.6 (q, s, t-Bu), 60.9 (q, OMe), 126.4, 128.7, 130.2, 131.4 (4 d, Ar), 138.4, 142.6 (2 s, Ar), 149.8, 159.3, 159.4, 166.9 (4 s, Py) \text{ ppm}; \text{ESI–TOF (m/z): } [\text{M} + \text{H}]^+ \text{ cale}d \text{ for } C_{32}H_{39}N_2O_4, 511.3068; \text{found, } 511.3085.
Supporting Information

Supporting Information File 1
Additional experimental procedures and analytical data, as well as copies of NMR spectra of representative examples.

[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-37-S1.pdf]

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