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LETTERS

A New and Convenient Synthesis of α-Tetramic Acid Amides via a Cobalt(II)-Mediated Reaction Cascade

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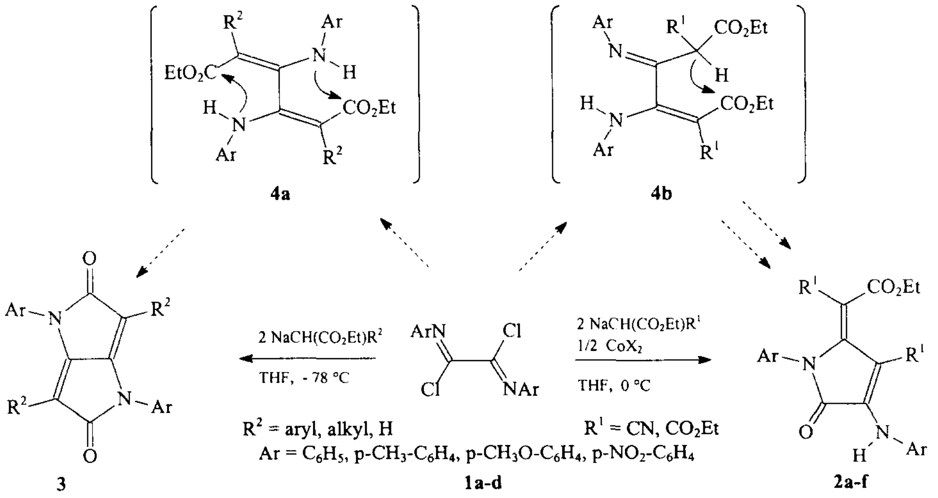
Abstract: A novel cobalt(II)-mediated domino reaction of carbon nucleophiles with **1a-d** has been developed. The resulting cyclization regioselectively yields functionalized α-tetramic acid amides.

α-Tetramic acid amides (2-oxo-3-amino-pyrrolid-5-enes) are N-heterocycles of pharmacological significance and valuable building blocks in the synthesis of a variety of alkaloid natural products.[1] The development of efficient methods for the construction of the α-tetramic acid amide core structure is thus of continuing interest.[2] Herein, we report a new cobalt(II)-mediated reaction cascade which readily yields this significant core structure.

For our starting reagents, we have chosen four different bis(imidoyl) dichlorides of oxalic acid **(1a-d)**[3] and various carbon nucleophiles. We have recently described the formation of pyrrolo[3,2-b]pyrrole-2,5-diones **3** only in THF at –78 °C using anions of alkyl and aryl substituted acetic esters.[4] Using such starting materials, however, employment of the anions of diethyl malonate or ethyl cyanoacetate gave under various reaction conditions (e.g. presence of base, under reflux) a complex reaction mixture only. Cyclization of an intermediate bis-enamine can, in principle, occur by attack of a nitrogen (s-trans bis-enamine **4a**) or a carbon atom (s-trans 3-amino-1-azadiene **4b**) on the ester carbon.



Scheme 1

PII: S0040-4039(97)10872-3

Clearly, a change in mechanism was required in order to obtain the desired α-tetramic acid amide framework; thus we have studied the effect of transition metals in fixing the 3-amino-1-azadiene configuration **4b** by chelation.[5]

Treatment of bis(imidoyl) dichlorides **1** (1.0 equiv.) with deprotonated ethyl cyanoacetate (2.0 equiv.) in the presence of cobalt(II) bromide or cobalt(II) chloride (0.5 equiv.) and an excess of $Na[N(SiMe_3)_2]$ (1.5 equiv.) resulted in regioselective cyclization giving α-tetramic acid amides **2a-c** after aqueous work up.[6] Likewise, reaction of deprotonated ethyl malonate yielded heterocycles **2d-f**.

Table 1: Synthesis of α-tetramic acid amides (2-oxo-3-amino-pyrrolid-5-enes) **2a-f**

$Cl_2C_2(N\text{-}Ar)_2$	**1a**	**1b**	**1c**	**1a**	**1c**	**1d**
Ar	$4\text{-}C_6H_4CH_3$	$p\text{-}C_6H_4OCH_3$	C_6H_5	$4\text{-}C_6H_4CH_3$	C_6H_5	$4\text{-}C_6H_4NO_2$
CoX_2	$CoBr_2$	$CoCl_2$	$CoBr_2$	$CoCl_2$	$CoBr_2$	$CoBr_2$
Product	**2a**	**2b**	**2c**	**2d**	**2e**	**2f**
R^1	CN	CN	CN	CO_2Et	CO_2Et	CO_2Et
Isolated Yield (%)	71	66	74	54	61	56

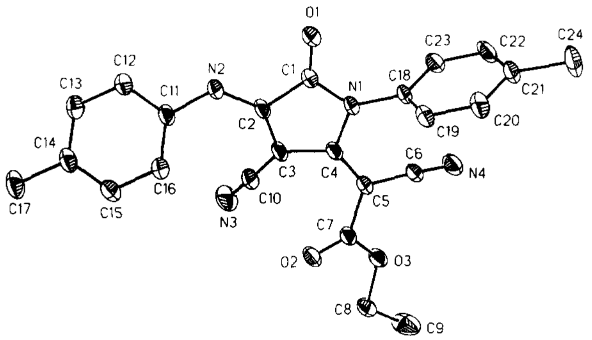
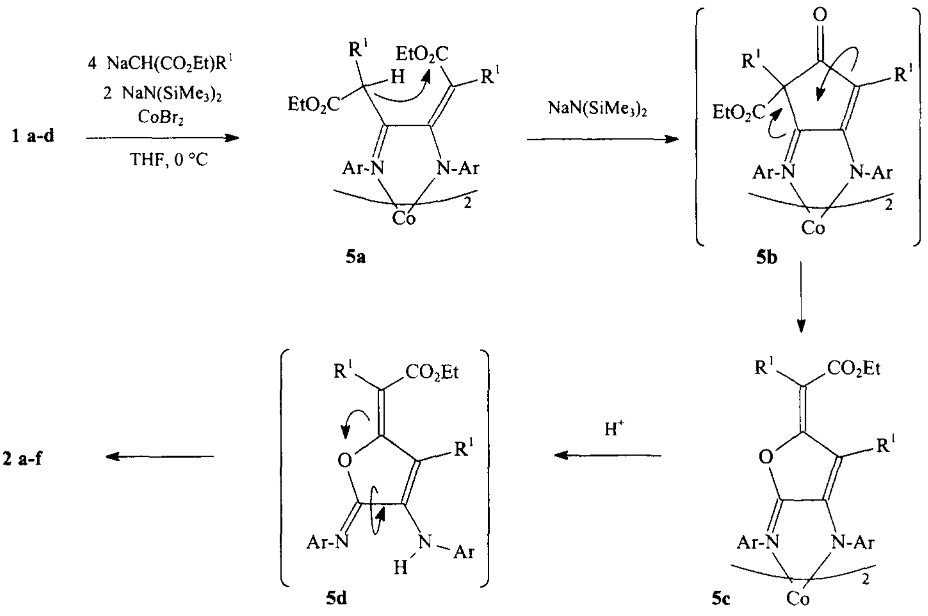


Figure 1: X-ray crystal structure of **2a**, selected bond length (Å): C1-O1, 1.207(2); C1-N1, 1.388(2); C4-N1, 1.396(2); C2-N2, 1.323(2); C2-C3, 1.379(2); C3-C4, 1.449(2); C3-C10, 1.425(2).

The structure of **2a** was confirmed by X-ray crystallographic analysis.[7] The exocyclic double bond C4-C5 possesses *E*-configuration and the aryl groups are twisted out of plane. The bond lengths C1-N1, C2-N2 and N1-C4 are decreased relative to C-N single bonds due to the amide resonance within the amide and the vinylogous amide functions. Bond length alternation is observed for the oxopyrrolidene **2a**.

Formation of α-tetramic acid amides **2a-f** can be rationalized by the following mechanism: Initial attack of the monoanions on the bis(imidoyl) dichloride **1** affords, in the presence of $CoBr_2$, intermediate complex **5a**. Induced by abstraction of the proton adjacent to the ester function by Na[N(SiMe$_3$)$_2$], cobalt(II) coordinated 3-amido-1-azadiene undergoes a Dieckmann condensation to give intermediate **5b** (being an unstable tetracarbonylmethane analogue). Rearrangement of the latter to **5c** and subsequent Dimroth rearrangement of **5d** in the course of aqueous work up finally affords oxopyrrolidenes **2a-f**. It is noteworthy that the cyclization does not proceed via attack of a nitrogen atom on the carbonyl group, as is the case in the formation of **3**. In contrast, the regiochemistry of cyclization is controlled by the coordination of the nitrogen atoms to the transition metal. The nitrogen atoms are not available for intramolecular attack on the ester function and, thus, the latter can only be attacked by the enolate carbon atom. Preliminary results support the mechanism suggested, as it was possible to isolate complexes **5a** (coordinated amido-azadiene) and **5c**. Hydrolysis of complex **5c** afforded α-tetramic acid amide **2a** in excellent yield (89%).



Scheme 2. Possible mechanistic scheme.

In summary, we have found a cobalt(II)-mediated domino cyclization reaction which includes six steps (C-C-coupling, complexation, Dieckmann condensation, rearrangement, decomplexation, Dimroth rearrangement). The reaction cascade regioselectively affords pharmacologically significant functionalized α-tetramic acid amides **2a-f** in an one-pot procedure from simple starting materials. Our current work is directed towards extending the preparative scope of the reaction presented to the synthesis of naturally occurring alkaloids, and towards exploring the mechanism of the cyclization.

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5. Complexation of 3-amino-1-azadiene (e.g. aminotropone iminates) to transition metals are known to proceed readily: G. M. Villacorta, S. J. Lippard *Pure Appl. Chem.* **1986**, *58*, 1477.
6. Spectroscopic data of **2a**: Starting with ethyl cyanoacetate (0.88 ml, 8 mmol) and **1a** (1.22 g, 4 mmol), 1.2 g of **2a** (71%) was isolated, red crystals, m.p. 279 °C; IR (nujol) 3247 (s), 2220 (m), 2204 (m), 1737 (s), 1706 (s), 1641 (s) cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d$_6$) δ 1.14 (t, 3 H, $\mathrm{CH_2C}H_3$), 2.30, 2.33 (s, 6 H, Tol-CH$_3$), 4.15 (q, 2 H, $\mathrm{C}H_2\mathrm{CH_3}$), 7.35 (m, 8 H, Tol), 11.34 (s, 1 H, NH); ^{13}C NMR (50 MHz, DMSO-d$_6$) δ_C 13.6 ($\mathrm{CH_2}C\mathrm{H_3}$), 20.9, 21.0 (Tol-CH$_3$), 61.7 ($C\mathrm{H_2CH_3}$), 75.4 (C, C-6), 79.8 (C, C-4), 112.4, 120.3 (C, CN), 122.8, 124.3, 129.1, 129.6, 130.0, 130.1 (C, CH, Tol), 133.6 (C, C-3), 133.1, 136.8 (C, Tol-C to N), 146.6 (C, C-5), 158.0, 162.7 (C, C-2, CO); MS(CI/H$_2$O): *m/e* 412(46%, (M+1)$^+$).
7. The crystal was measured on Enraf-Nonius CAD4 four circle diffractometer using ω–2θ scan mode. The structure was solved by direct methods (SHELXS) and refined against F^2 (SHELXC-93).

   Crystal data for **2a•DMF**: $C_{27}H_{27}N_5O_4$, red prism, size 0.40 x 0.38 x 0.38 mm, Mr = 485.54 gmol^{-1}, triclinic, space group P1, a = 9.241(5), b = 11.100(5), c = 13.854(5) Å, α = 68.090(5)°, β = 76.180(5)°, γ = 84.820(5)°, V = 1280.3(10) Å^3, Z = 2, $\rho_{calcd.}$ = 1.26 gcm^{-3}, μ (Mo-K$_\alpha$) = 0.73 cm^{-1}, F(000) = 512, 6189 reflections in ±h, ±k, +l, measured in the range 2.27° ≤ Θ ≤ 27.41, 5816 independent reflections, R_{int} = 0.0404 , 5814 reflections with $F_o > 4\sigma(F_o)$, 434 parameter, R = 0.048 and wR^2 = 0.127, GOOF: 1.17, largest difference peak 0.31 eÅ^{-3}. The atomic co-ordinates for this work are available from the Director of the Cambridge Cristallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.