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Synthesis of Chiral Chromium Tricarbonyl Labeled Thymine PNA Monomers via the Ugi Reaction

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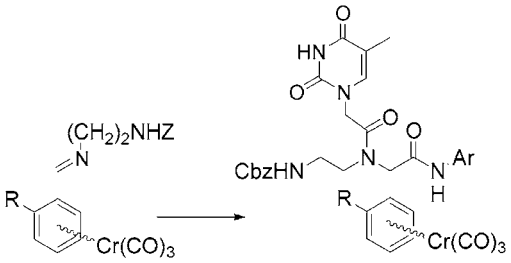
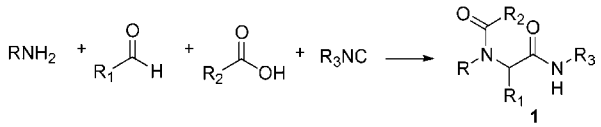
ABSTRACT



Ugi condensation was used to synthesize the first examples of chiral racemic Ar·Cr(CO)$_3$ labeled peptide nucleic acid (PNA) monomers bearing the organometallic moiety linked to the α-carbon of the glycine unit.

The Ugi four-component reaction (U-4CR), in which an amine, a carbonyl compound, a carboxylic acid, and an isocyanide react in a one-pot process (Scheme 1), is a convenient method of achieving the α-acylamino amides **1**, generally in good yields.[1]

Scheme 1



Because of the possibility of using a large number of different components, the U-4CR has recently been used to build large libraries and applied to the synthesis of peptide nucleic acid (PNA) monomers.[2] PNAs are DNA mimics containing a pseudopeptide backbone, and interest in their therapeutic and diagnostic applications is rapidly growing as they show high binding affinity and selectivity to complementary DNA and RNA.[3]

We have recently been interested in making modified PNAs and have particularly focused on the synthesis of organometallic conjugates in order to (i) exploit our expertise in stereoselective synthesis using chiral Cr(CO)$_3$ complexes[4] to obtain chiral PNA organometallic conjugates and (ii) use the unique spectroscopic and reactivity properties of organometallic compounds to confront biological and biomedical issues such as the possible improvement of cell permeability (which is poor for PNAs), the resolution of analytical problems (use of PNAs as spectroscopic and electrochemical probes),[5] and possibly the induction of different specificities in binding properties with DNA and RNA.

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Metzler-Nolte has recently described the synthesis of a PNA monomer **2** (Figure 1) labeled with transition metals at the terminal nitrogen of the aminoethyl residue, to be used as a spectroscopic and electrochemical probe.[6]

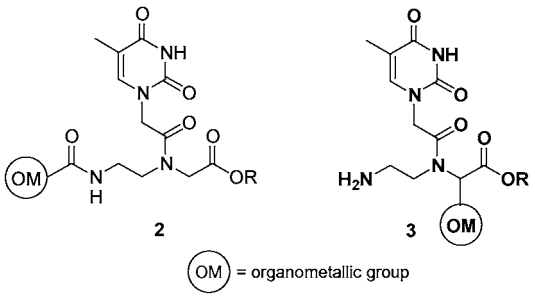
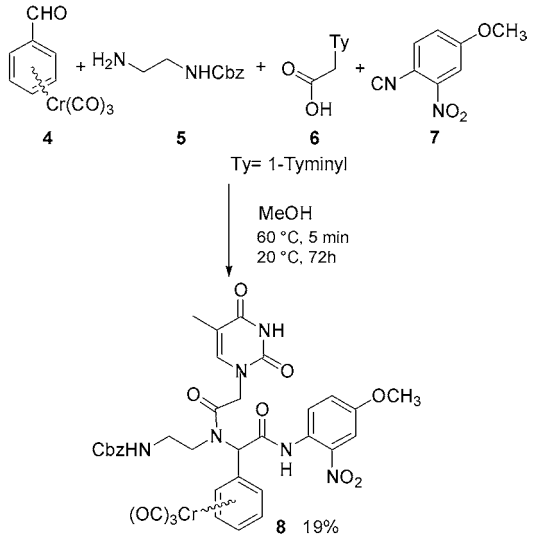


Figure 1.

Our idea was to synthesize a PNA monomer **3** (Figure 1) in which the organometallic moiety is linked to the α-carbon of the glycine unit, thus retaining the aminoethylglycine function that can be used for the further construction of an oligomer, either through an iterative replication of **3** along the chain or by including monomer **3** into a traditional PNA chain. These organometallic conjugates are expected to show greater lipophilic character and a better cell permeability in comparison with that of classic PNAs. In addition the detection of strong IR bands of the metal CO groups (2000−1850 cm^{-1}) could provide a useful and easy handle for the molecular recognition of specific DNA sequences. Moreover, chiral PNAs are generated, and as for other nucleotide analogues, the chirality in a PNA strand can affect DNA interaction and binding properties. Some examples of chiral PNAs have been reported,[7] but the problem of their enantioselective synthesis deserves further attention. Chiral organometallic complexes have never been used as carbonyl components in Ugi condensations, and the prospect of obtaining a PNA monomer in a one-pot stereoselective reaction was highly attractive.[8] To this end, we considered chiral benzaldehyde chromiumtricarbonyl complexes for a stereoselective version of the Ugi reaction because they can be easily obtained in enantiopure form[9] and usually lead to high stereoselectivity.[10]

To set up the experimental conditions, the 4-component reaction was first run using benzaldehyde·$Cr(CO)_3$ **4** as model compound (Scheme 2). The other components were

Scheme 2. Ugi Reaction on Benzaldehyde Complex **4**



N-Cbz-ethylendiamine **5**, 1-carboxymethylthymine **6**, and 4-methoxy-2-nitrophenyl isonitrile **7**. We chose this isonitrile[11] (the precursor of the arylamide function in compound **8**) in order to hydrolyze the amido group under basic conditions[2] compatible with the presence of the $Cr(CO)_3$ group. The Cbz protection at the nitrogen of ethylendiamine **5** was chosen for the same reason.

In accordance with the conditions patented by Ugi et al.,[12] the reaction was run in MeOH with an equimolar mixture of the four reagents. The reaction time (72 h) represents the best compromise between yield and stability of the complexed monomer precursor **8**. After a standard workup followed by chromatographic separation, **8** was isolated in 19% yield. No improvement in reaction yield was obtained by changing time, solvent, or temperature; more prolonged heating led to the decomposition of the products.

As the Ugi reaction with Cbz-protected ethylendiamine is not reported in the literature, for the sake of comparison we repeated the reaction on the uncomplexed benzaldehyde **9** under the same conditions. (Scheme 3). The corresponding product **10** was isolated in 22% yield, which is comparable with that of the reaction on complex **4** but less than that reported using the *N*-Boc protected ethylendiamine (41%).[2b]

To improve the reaction yields,we then tried the condensation on the preformed imine **11** (Scheme 4), which was obtained in quantitative yields from the benzaldehyde

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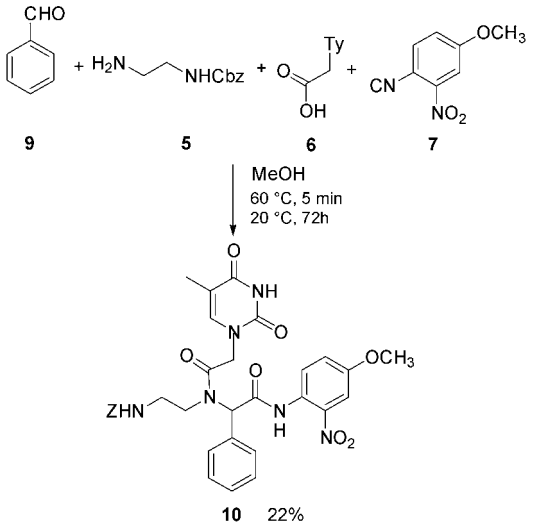
(11) Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 2574.

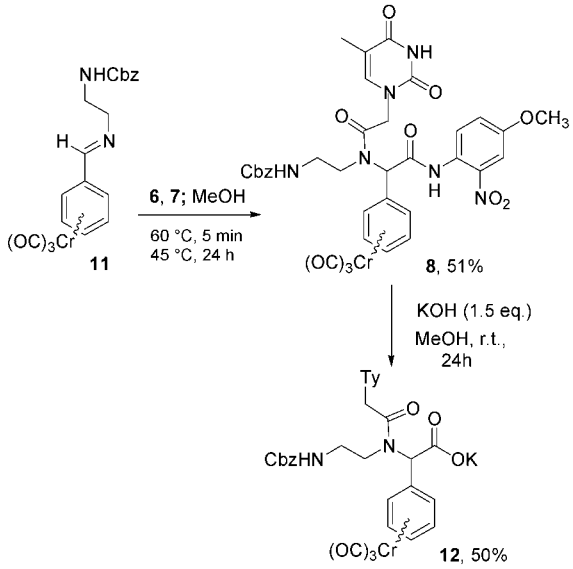
(12) Domling, Alexander; Richter, Wolfgang PCT Int. Appl., 1998.

Scheme 3. Ugi Reaction on Benzaldehyde **9**



complex **4** and amine **5** by heating at 30 °C in EtOH for 8 h. In this case, under the same conditions as those reported in Scheme 1, product **8** was isolated after column chromatography in 50% yield.[13]

Scheme 4. Ugi Reaction on Benzaldimine Complex **11**

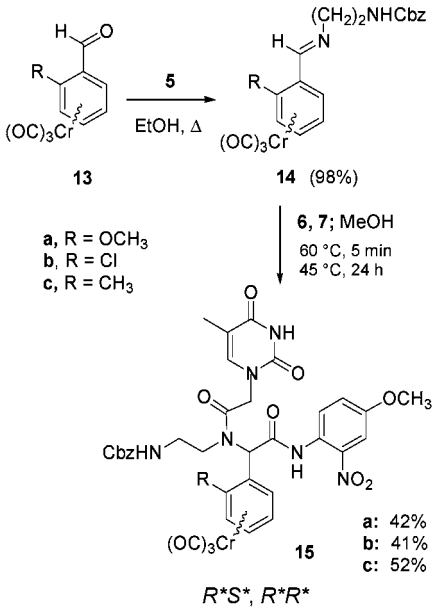


In addition, a preliminary experiment of the hydrolysis of the *N*-aryl amide function was run in MeOH using 1.5 equiv of ground KOH. (Scheme 4). The reaction was not optimized and the PNA monomer **12** was isolated as potassium salt in 50% yield.[14]

(13) **Typical Procedure.** An equimolar mixture of benzaldimine complex **11** (1.1 mmol), 1-carboxymethylthymine **6**, and 4-methoxy-2-nitrophenylisonitrile **7** in MeOH (4 mL) was heated under nitrogen at 45 °C for 24 h and then stirred at room temperature for 3 days. After evaporation of the solvent, the crude product was purified by column chromatography (AcOEt) to afford **8** as a yellow powder. Mp 124−125 °C (pentane). Anal. Calcd for $C_{35}H_{32}CrN_6O_{12}$: C, 53.85; H, 4.13; N, 10.77. Found: C, 53.42; H, 4.16; N, 10.78. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80 (s, 3H, CH_3), 3.28−3.58 (m, 2H, NCH_2CH_2N), 3.95−3.68 (m, 2H, NCH_2CH_2N), 3.82 (s, 3H, OCH_3), 4.22 (d, 1H, J = 16.4 Hz, CH_2CO), 4.46 (s, 1H, CH), 4.60 (d, 1H, J = 16.4 Hz, CH_2CO); 5.22−5.28 (m, 4H, CH_2O + 2H $PhCr(CO)_3$), 5.56 (d, 1H, J = 5.5 Hz, $PhCr(CO)_3$), 5.64 (dd, 1H, $J_1 = J_2$ 6.3 Hz, $PhCr(CO)_3$), 5.80 (d, 1H, J = 6.3 Hz, $PhCr(CO)_3$), 5.99 (s, 1H, NH), 6.58 (s, 1H, CH=), 7.19 (dd, 1H, J = 2.9, 9.4 Hz, arom), 7.27−7.40 (5H, m, Ph), 7.60 (d, 1H, J = 2.9 Hz, arom), 8.51 (d, 1H, J = 9.4 Hz, arom), 8.55 (s, 1H, NH), 10.30 (s, 1H, NH). ^{13}C NMR (300 MHz, $CDCl_3$) δ 231.9, 168.5, 166.6, 164.2, 156.7, 155.8, 150.9, 140.9, 137.8, 136.3, 128.9, 128.1, 124.0, 123.1, 110.6, 108.9, 99.8, 97.2, 96.5, 95.6, 89, 88.9, 67.1, 65.9, 55.9, 48.8, 48.0, 39.5, 12.3. IR (Nujol, ν cm^{-1}) 1877, 1968, 1681.

As one of the targets of the present study was to obtain an enantiopure PNA monomer, the Ugi condensation was then studied on chiral racemic ortho-substituted benzaldimine complexes **14a**−**c**, which were again obtained in quantitative yields from benzaldehyde complexes **13a**−**c** and amine **5**. (Scheme 5).

Scheme 5. Ugi Reaction on Chiral Benzaldimine Complexes **14 a**−**c**



The first condensation was run on complex **14a** under the above conditions and afforded monomer **15a** in 42% yield as a mixture of the two diastereoisomers in a 55:45 ratio.

The lack of stereoselectivity was rather unexpected, as the use of ortho-substituted complexes usually leads to very high diastereoselections, in accordance with the stereochemical model known for such complexes.[9] To investigate the role of the ortho substituent in the stereochemical outcome of the condensation, the reaction was extended to 2-Cl and 2-methylbenzaldimine complexes **14b,c**. In both cases, an almost equimolar ratio of the two diastereoisomers was again obtained in 41% and 52% yields.[15]

(14) The hydrolytic step is crucial for the synthesis of enantiopure PNAs because of the presence of a benzyl proton that might lead to racemization in basic medium. However, it has been reported that deprotonation and subsequent electrophilic quenching at the benzylic position of arene chromiumtricarbonyl derivatives proceeds stereopecifically. See: Davies, S. G.; Blagg, J. *Tetrahedron* **1987**, *41*, 4463.

As the nature of the ortho substituent does not affect stereoselection, it is reasonable to suppose that the heating necessary to promote the reaction prevents any chiral discrimination between the two diastereofaces of the imine moiety. On the other hand, the reaction does not run at room temperature.

It is worth noting that, in all cases, the two diastereoisomers can be separated by column chromatography. Thus, when starting from enantiopure benzaldehyde complexes **13a**−**c**, it is possible to obtain both enantiomers of **15a**−**c** in a one-pot process and in good yields in comparison with the classical multistep synthesis of a PNA monomer.[16]

(15) Comparable yields were obtained from the reaction on the corresponding uncomplexed imine.

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Supporting Information Available: Experimental details and analytical and spectroscopic data of imines **11** and **14a**−**c** and of monomers **10**, **12**, and **15 a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026994A

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