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New cleavable isocyanides for the combinatorial synthesis of α-amino acid analogue tetrazoles

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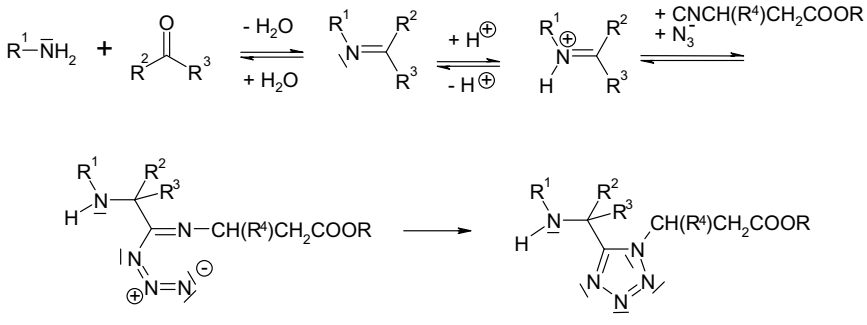
This paper is dedicated to Professor Ivar K. Ugi on his 75th birthday

Abstract—3-Substituted 3-isocyano propionates as new cleavable isocyanides in combinatorial tetrazole synthesis via Ugi-reaction are introduced. The obtained 5-substituted tetrazoles are transformed into carboxylic acid isosteric 5-substituted 1*H*-tetrazoles under basic cleavage conditions.

In 1956, Herbst suggested that in biologically active carboxylic acids, the replacement of carboxyl group with a 5-tetrazolyl group may create compounds with interesting properties.[1] Therefore, many amino acid analogous tetrazoles were synthesized.[2,3] In these, carboxylic group is isosterically replaced by a 5-tetrazolyl group[4,5] to produce amino acids analogues.

The earliest published methods for the preparation of 5-substituted tetrazoles were reactions of nitriles with azides.[6] Until now most methods are based on nitriles, so these are the limiting compounds for structural diversity. Therefore, Ugi and Steinbrückner developed the first multicomponent reaction (MCR) yielding bis-substituted tetrazoles, which gives a versatile access to an enormous structural diversity in a simple one-pot procedure. Mixing an oxo-component, an amine, trimethylsilyl azide (as hydrazoic acid equivalent) and isocyanide in a ratio of 1/1/1.5/1.5 in methanol leads to the formation of the tetrazoles in the MCR (Scheme 1). This reaction is initiated by condensation of an appropriately substituted aldehyde or ketone with a reactive amine. Subsequent reaction with isocyanide produces the intermediate nitrilium ion, as a key intermediate. The desired



Scheme 1. Mechanism of tetrazole-U-4CR.

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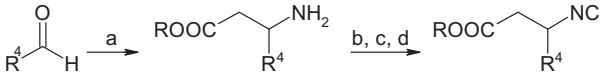
tetrazole is obtained by reaction with the azide, followed by sigmatropic rearrangement.[7,8]

In 1964, Ugi and Offermann[9] described amines with an acidic proton in β-position to amino group as cleavable amine components in MCRs. Abstraction of the acidic β-H with alkoxides leads to elimination of stable α-β-unsaturated esters. We decided to apply the same principle to our new corresponding isocyanides analogously.

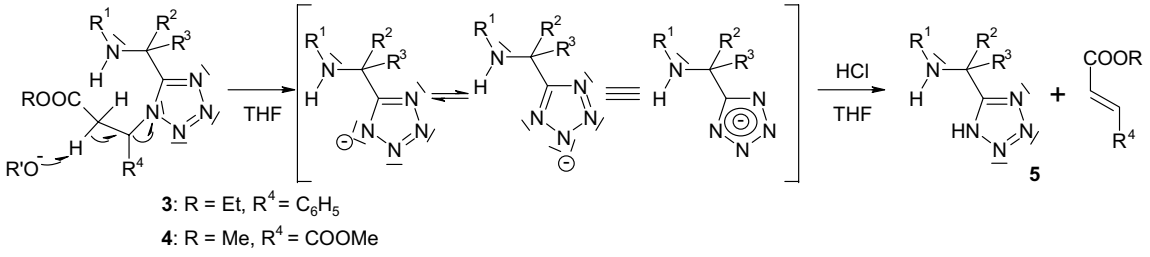
The sequence of tetrazole-U-4CR using our new isocyanides followed by basic cleavage of this isocyanide moiety leads to 1*H*-tetrazoles in an easy way.

The new cleavable isocyanide 3-isocyano-3-phenyl-ethylpropionate **1** is synthesized starting with β-amino acid obtained by an α-amino alkylation.[10] This compound is esterified in ethanol with thionyl chloride. After formylation in ethyl formate, the isocyanide is obtained by dehydration in a two-step procedure. First, the formamide solved in dry methylene chloride is treated with phosphoryl chloride in the presence of triethylamine. When the reaction is finished, an aqueous solution of sodium carbonate is added. After extraction, the pure product is obtained by distillation (Scheme 2).[11–13] 2-Isocyano succinic acid dimethylester **2** is synthesized in the same way (with R = Me), starting with commercially available aspartic acid.

Using isocyanides **1** and **2** several 5-substituted tetrazoles **3a–h** and **4i–k**[14]—bearing three points of diversity—are synthesized in good yields (Table 1). Upon treatment with an alkoxide base 5-substituted 1*H*-tetrazoles **5a–k**[15] (Table 1) are obtained. The proposed β-elimination mechanism is also promoted by mesomeric stabilization of the delocalized charge over the whole tetrazole ring system (Scheme 3). Using potassium *tert*-butoxide the cleavage is faster, attaining higher yields in comparison to sodium ethanolate. With ethanolate base the reaction conditions are slightly milder especially for compound **3d** and **e**, where otherwise partial cleavage of the acetal group and consecutive reactions were observed.

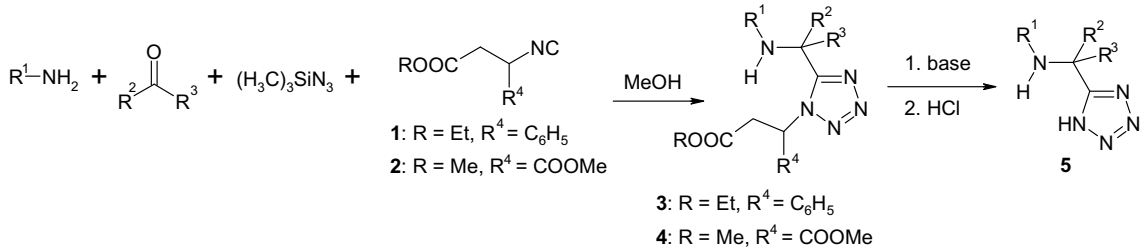


Scheme 2. Synthesis of the isocyanides. Reagents: (a) NH_4OAc, malonic acid, MeOH; (b) $SOCl_2$, ROH; (c) Et_3N, ROCHO; (d) (1) $POCl_3$, Et_3N, CH_2Cl_2, (2) Na_2CO_3, H_2O.



Scheme 3. Proposed cleavage mechanism of the isocyanide moiety by β-elimination.

Table 1. Synthesized tetrazoles **5a–k**



R^1	R^2	R^3	R^4	R	Yield (%)	Product	Base	Yield (%)	Product
$PhCH_2$	$(CH_3)_2CH$	H	C_6H_5	Et	89	**3a**	NaOEt	33	**5a**
$PhCH_2$	*p*-$MeOC_6H_4$	H	C_6H_5	Et	83	**3b**	NaOEt	45	**5b**
$PhCH_2$	*p*-$BOCNHC_6H_4$	H	C_6H_5	Et	92	**3c**	NaOEt	56	**5c**
$(MeO)_2CHCH_2$	Ph	H	C_6H_5	Et	65	**3d**	NaOEt	65	**5d**
$(MeO)_2CHCH_2$	*p*-$MeOC_6H_4$	H	C_6H_5	Et	40	**3e**	NaOEt	36	**5e**
p-$MeOCOC_6H_4$	$(CH_3)_2CH$	H	C_6H_5	Et	37	**3f**	KO-*t*-Bu	47	**5f**
Ph_2CH	$(CH_3)_2CH$	H	C_6H_5	Et	42	**3g**	NaOEt	65	**5g**
$PhCH_2$	Me	Me	C_6H_5	Et	67	**3h**	KO-*t*-Bu	37	**5h**
$PhCH_2$	$(CH_3)_2CH$	H	COOMe	Me	77	**4i**	KO-*t*-Bu	42	**5i**
$PhCH_2$	Ph	H	COOMe	Me	88	**4j**	KO-*t*-Bu	67	**5j**
$PhCH_2$	Me	Me	COOMe	Me	73	**4k**	KO-*t*-Bu	55	**5k**

In summary, combinatorial synthesis of 5-substituted tetrazoles with new cleavable isocyanides has been reported. With final products containing three points of potential diversity, access to huge amount of diverse analogues is now feasible. Current efforts are now focusing on the diverse combinations of cleavable amines and the described isocyanide components in Ugi-tetrazole-MCR widening the domain of 1*H*-tetrazoles.

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13. Procedure for isocyanides **1** and **2**: 0.1 mol $POCl_3$ are added dropwise to 0.1 mol of the 3-formylamino alkyl propionate, solved in 100 mL dry CH_2Cl_2, in the presence of 0.248 mol triethylamine. After stirring 1 h the reaction mixture is treated with 20 g Na_2CO_3 in 80 mL water at 20–25 °C. After stirring 1 h the deposit is filtered off. The separated dichloromethane layer is washed three times with brine and dried over K_2CO_3. The solvent is reduced in vacuo.
    Compound **1** was obtained as a transparent, colourless liquid in a yield of 46% by distillation (bp: 110 °C/1.8×10^{-2} mbar). ^{1}H NMR ($CDCl_3$, 250.13 MHz): 1.26 (t, 3H, $^2J = 14.19$ Hz, $^3J = 7.02$ Hz, –COOCH$_2$C*H*$_3$), 2.95 (dd, 2H, $^2J = 16.02$ Hz, $^3J = 8.85$ Hz, –C*H*$_2$COOEt), 4.20 (q, 2H, $^3J = 7.17$ Hz, –COOC*H*$_2$CH$_3$), 5.18 (t, 1H, $^3J = 8.24$ Hz, –C*H*NC), 7.38 (s, 5H, –C$_6$*H*$_5$). ^{13}C NMR ($CDCl_3$, 62.89 MHz): 14.0 (–COOCH$_2$*C*H$_3$), 43.4 (–*C*H$_2$COOEt), 54.7 (–*C*HNC), 61.2 (–COO*C*H$_2$CH$_3$), 125.9, 128.7, 129.0, 136.0 (–*C*$_6$H$_5$), 158.2 (–N*C*), 168.7 (–*C*OOEt).
    Compound **2** was obtained as a pale yellow oil in a yield of 41% by distillation (bp: 127 °C/1.8×10^{-2} mbar). ^{1}H NMR ($CDCl_3$, 250.13 MHz): 3.02 (dd, 2H, $^2J = 12.50$ Hz, $^3J = 5.80$ Hz, –C*H*$_2$–), 3.77 (s, 3H, –CH$_2$-COOC*H*$_3$), 3.87 (s, 3H –COOC*H*$_3$), 4.69 (t, 1H, $^3J = 6.04$ Hz, –C*H*NC).
14. Typical procedure for synthesis of tetrazoles **3** and **4**. Aldehyde (10 mmol) and amine (10 mmol) are stirred in 10 mL methanol at room temperature for 1 h and then 15 mmol of trimethylsilyl azide and 15 mmol of isocyanide are added. The reaction mixture is stirred for 48 h at room temperature until the reaction is completed (indication by TLC). Then the solvent is removed under vacuum and the resulting residue is purified by column chromatography on silica gel with hexane/ethyl acetate (1:1).
    Compound **3a** was isolated in 89% yield as a white solid. ^{1}H NMR ($CDCl_3$, 360.13 MHz): 0.47 [d, $^3J = 6.58$, 3H, –CH(C*H*$_3$)$_2$], 0.76 [d, $^3J = 6.58$, 3H, –CH(C*H*$_3$)$_2$], 1.17 (t, $^3J = 7.27$ Hz, $^2J = 14.5$ Hz, 3H, –COOCH$_2$C*H*$_3$), 1.95 [m, 1H, –C*H*(CH$_3$)$_2$], 2.96 (d, $^2J = 13.2$ Hz, 1H, –NHC*H*$_2$Ph), 3.11 (dd, $^3J = 5.0$ Hz, $^2J = 12.02$ Hz, 1H, –C*H*$_2$COOEt), 3.17 (dd, $^3J = 4.99$ Hz, $^2J = 12.02$ Hz, 1H, –C*H*$_2$COOEt), 3.37 (d, $^2J = 13.2$ Hz, 1H, –C*H*$_2$NH–), 3.74 [m, 1H, –C*H*-(NHCH$_2$Ph)(CHMe$_2$)], 4.08 (m, 2H, –COOC*H*$_2$CH$_3$), 5.87 [dd, $^3J = 5.0$ Hz, $^3J = 4.99$ Hz, 1H, –C*H*(Ph)CH$_2$-COOEt], 6.99–7.34 (m, 10H, –C$_6$*H*$_5$). ^{13}C NMR ($CDCl_3$, 90.56 MHz): 13.8 (–COOCH$_2$*C*H$_3$), 18.5 [–CH(*C*H$_3$)$_2$], 19.2 [–CH(*C*H$_3$)$_2$], 31.9 [–*C*H(CH$_3$)$_2$], 40.9 (–*C*H$_2$COOEt), 50.9 (–*C*H$_2$C$_6$H$_5$), 57.4 (–*C*H(Ph)CH$_2$COOEt), 58.8 [–*C*H-(NHCH$_2$Ph)(CHMe$_2$)], 61.0 (–COO*C*H$_2$CH$_3$), 126.5, 126.9, 127.8, 128.0, 128.2, 129.0, 137.3, 139.4 (–*C*$_6$H$_5$), 156.9 [–*C*N$_4$CH(Ph)CH$_2$COOEt], 170.8 (–*C*OOEt). MS (ESI): $m/z = 408.3$ $[M+1]^+$, 430.2 $[M+Na]^+$.
    Compound **3b** was isolated in 83% yield as a yellow oil. ^{1}H NMR ($CDCl_3$, 250.13 MHz): 1.15 (m, 3H, –COO-CH$_2$C*H*$_3$), 3.01 (m, 1H, –C*H*$_2$COOEt), 3.09 (m, 1H, –CH$_2$COOEt), 3.45 (m, 2H, –NHC*H*$_2$Ph), 3.75 (s, 3H, –OC*H*$_3$), 3.98 (q, $^3J = 7.02$ Hz, 2H, –COOC*H*$_2$CH$_3$), 5.03 [s, 1H, –C*H*(NHCH$_2$Ph)C$_6$H$_4$OMe], 5.81 (m, 1H, –C*H*(Ph)CH$_2$COOEt), 6.72–7.39 (m, 14H, –*C*$_6$H$_5$, –*C*$_6$H$_4$). ^{13}C NMR ($CDCl_3$, 62.90 MHz): 13.9 (–COO-CH$_2$*C*H$_3$), 40.6 (–*C*H$_2$COOEt), 51.0 (–NH*C*H$_2$Ph), 55.2 (–O*C*H$_3$), 55.5 [–*C*H(Ph)CH$_2$COOEt], 58.4 [–*C*H(NH-CH$_2$Ph)C$_6$H$_4$OMe], 61.2 (–COO*C*H$_2$CH$_3$), 114.2, 126.5, 126.8, 127.2, 128.1, 128.4, 128.5, 128.8, 129.3, 136.4, 138.9, 159.6 (aryl), 156.0 [–*C*N$_4$CH(Ph)CH$_2$COOEt], 169.2 (–*C*OOEt). MS (ESI): $m/z = 472.2$ $[M+1]^+$, 494.1 $[M+Na]^+$.
    Compound **3e** was isolated in 40% yield as a yellow oil. ^{1}H NMR ($CDCl_3$, 250.13 MHz): 1.11 (t, $^3J = 7.02$ Hz, $^2J = 14.3$ Hz, 3H, –COOCH$_2$C*H*$_3$), 2.48 (dd, $^3J = 5.49$ Hz, $^2J = 11.9$ Hz, 1H, –C*H*$_2$COOEt), 2.59 (dd, $^3J = 5.5$ Hz, $^2J = 11.9$ Hz, 1H, –C*H*$_2$COOEt), 3.27 [s, 3H, –CH-(OC*H*$_3$)$_2$], 3.28 [s, 3H, –CH(OC*H*$_3$)$_2$], 3.50 [m, 2H, –NHC*H*$_2$CH(OMe)$_2$], 4.00 (q, $J = 7.02$ Hz, 2H, –COO-C*H*$_2$CH$_3$), 4.39 [m, 1H, –C*H*(Ph)CH$_2$COOEt], 5.03 [s, 1H, –C*H*(C$_6$H$_4$OMe)NHCH$_2$CH(OMe)$_2$], 7.14–7.39 (m, 9H, –C$_6$*H*$_4$, –C$_6$*H*$_5$). ^{13}C NMR ($CDCl_3$, 62.90 MHz): 13.9 (–COO*C*H$_3$CH$_2$), 40.9 (–*C*H$_2$COOEt), 48.6 [–NH*C*H$_2$-CH(OMe)$_2$], 53.7, 53.9 [–CH(O*C*H$_3$)], 55.3 (–O*C*H$_3$), 56.9 [–C*H*(Ph)CH$_2$COOEt], 58.6 [–C*H*(C$_6$H$_4$OMe)NHCH$_2$-CH(OMe)$_2$], 61.1 (–COO*C*H$_2$CH$_3$), 103.6 [–*C*H(OCH$_3$)$_2$], 114.3, 126.7, 128.8, 129.1, 137.0, 159.7 (aryl), 155.9 [–*C*N$_4$CH(Ph)CH$_2$COOEt], 169.2 (–*C*OOEt). MS (ESI): $m/z = 470.2$ $[M+1]^+$, 492.3 $[M+Na]^+$.
15. Typical procedure: to 1 mmol of **3a**–**h** or **4i**–**k** in dry tetrahydrofuran 1.2 equiv of the base are added under nitrogen atmosphere. After stirring overnight, the mixture is neutralized with hydrochloric acid. Then solvent is removed under vacuum and water is added. This residue is extracted with ethyl acetate three times. The combined organic layers are dried, concentrated and finally dried under vacuum.
    Compound **5a** was isolated in 33% yield as a white solid. ^{1}H NMR (D_2O, 360.13 MHz): 0.75 [d, $^3J = 6.8$ Hz, 3H, –CH(C*H*$_3$)$_2$], 0.81 [d, $^3J = 6.8$ Hz, 3H, –CH(C*H*$_3$)$_2$], 2.35 [m, 6.4 Hz, 1H, –C*H*(CH$_3$)$_2$], 4.07 (s, 2H, –NHC*H*$_2$Ph), 6.54 [d, $^3J = 6.4$ Hz, 1H, –C*H*(NHCH$_2$Ph)(CHMe$_2$)], 7.17–7.35 (m, 5H, –C$_6$*H*$_5$). ^{13}C NMR (D_2O/1% D_3COD, 90.56 MHz): 17.6 [–CH(*C*H$_3$)$_2$], 19.8 [–CH(*C*H$_3$)$_2$], 31.8 [–*C*H(CH$_3$)$_2$], 51.7 (–*C*H$_2$Ph), 59.3 [–*C*H(NHCH$_2$Ph)-(CHMe$_2$)], 129.9, 130.8, 131.4, 131.7 (–*C*$_6$H$_5$), 155.9 (–*C*N$_4$H). MS (ESI): $m/z = 231.3$ $[M+1]^+$, 253.2 $[M+Na]^+$.
    Compound **5b** was isolated in 30% yield as a white solid. ^{1}H NMR (DMSO, 250.13 MHz): 3.55 (s, 2H, –C*H*$_2$Ph), 3.69 (s, 3H, –OC*H*$_3$), 4.87 [s, 1H, –C*H*(NHCH$_2$-Ph)C$_6$H$_4$OMe], 6.80 (d, $J =$ 8.54 Hz, 2H, –C$_6$*H*$_4$),

7.23–7.31 (m, 7H, $-C_6H_4$, $-C_6H_5$). ^{13}C NMR (DMSO, 69.90 MHz): 50.5 ($-CH_2Ph$), 55.0 ($-OCH_3$), 57.4 [$-CH(NHCH_2Ph)C_6H_4OMe$], 113.1, 126.4, 127.9, 128.1, 128.9, 135.9, 140.9, 163.4 ($-C_6H_4$, $-C_6H_5$), 157.8 (s, $-CN_4H$). MS (ESI): $m/z = 296.3$ $[M+1]^+$, 317.2 $[M+Na]^+$.

Compound **5k** was isolated in 55% yield as a white solid. ^1H NMR (DMSO, 250.13 MHz): 1.74 [s, 6H, $-C(CH_3)_2$], 3.90 (s, 2H, $-CH_2Ph$), 7.37 (m, 5H, $-C_6H_5$). ^{13}C NMR (DMSO 62.90 MHz): 25.3 [$-C(CH_3)_2$], 46.0 ($-CH_2Ph$), 128.4, 129.8, 133.7 (aryl), 161.6 ($-CN_4H$). MS (ESI): $m/z = 232.3$ $[M+1]^+$, 254.2 $[M+Na]^+$.