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# Synthesis of tetrazolopiperazine building blocks by a novel multi-component reaction

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**Abstract**—A novel Ugi-five-centre-four-component reaction (U-5C-4CR) of aldehydes, primary amines, trimethylsilylazide and 2-isocyanoethyltosylate yielding tetrazolopiperazine building blocks is described.


Combinatorial chemistry has recently gained much attention in pharmaceutical research, especially in the context of lead finding and lead optimization.[1–3] Multi-component reactions (MCRs) allow rapid generation of compound libraries containing a variety of different and highly relevant organic-chemical scaffolds.[4–10] Intending to the 'ideal' organic reaction[11] the discovery and development of novel MCRs is receiving a growing interest from industrial chemistry research groups.[12]

Therefore we present a novel, facile Ugi-five-centre-four-component reaction (U-5C-4CR) yielding 6,7-disubstituted-tetrazolopiperazines, which represents an extension of fused tetrazole synthesis, developed by Hulme and co-workers.[13] The formation of monocyclic tetrazoles was originally reported in 1961[14,15] using a variation of classical Ugi reaction. Condensation of an aldehyde or ketone with a primary or secondary amine and subsequent reaction with an isocyanide produces the intermediate nitrilium ion **1**, as a key intermediate. Reaction with azide, followed by sigmatropic rearrangement affords the desired tetrazole **3** (Scheme 1).

Several combinatorial synthesis of fused tetrazole systems by the use of post-condensation reaction are described,[13,16] but we are aiming at novel MCR, forming fused tetrazolopiperazines by the use of alkylating isocyanides. Therefore we mixed in a typical procedure[17] aldehydes, primary amines, trimethylsilylazide and 2-isocyanoethyltoluolsulfonate in a ratio 1/1/1.5/1.5, yielding the desired tetrazolopiperazines (Scheme 2).

An analogue reaction mechanism like in Scheme 1 is proposed, but the generated secondary amine finally gets alkylated by the toluolsulfonate, leading to the expected fused tetrazoles **5a**–**i** (Table 1).[18]

In this paper we show an efficient synthesis of various types of 6,7-disubstituted tetrazolopiperazines (Table 1) using 2-isocyanoethyltosylate **8** as alkylating isocyanide, which can be synthesized in two steps from 2-aminoethanole **6**[19] (Scheme 3).

In this new four-component reaction the primary amines and the aldehydes can be varied broadly, producing products with two potential diversity points.

In summary, a novel one-pot solution phase procedure for the preparation of 6,7-disubstituted tetrazolopiperazine building blocks has been reported. With final products containing two points of potential diversity and a facile and rapid production protocol, access to thousands of diverse analogues with the aforementioned core structure is now feasible.

Work is in progress in our laboratory to synthesize 1,2-disubstituted 2-isocyanoethyl-tosylates, finally creating tetrazolopiperazines with four points of diversity.

*Keywords*: Ugi-reaction; Tetrazolopiperazines; Combinatorial chemistry; Isocyanoethyltosylate.
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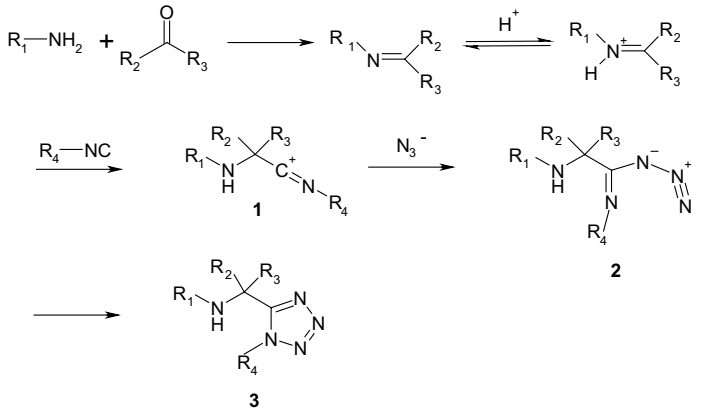
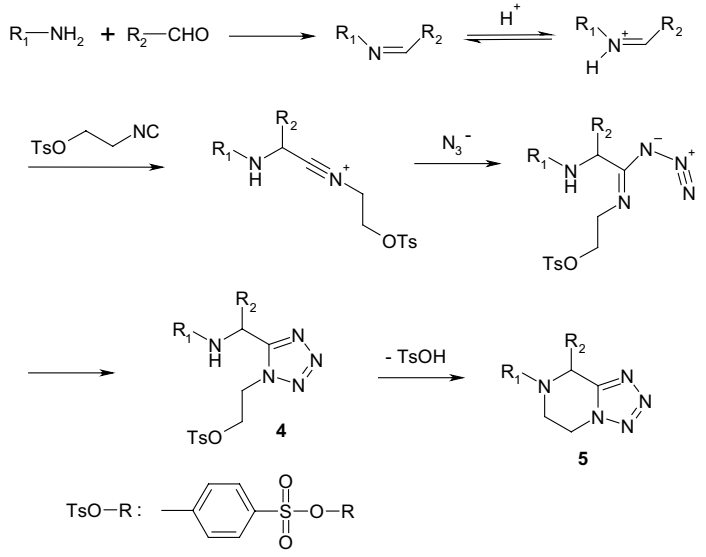
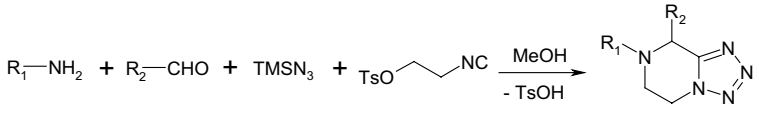


**Scheme 1.** Mechanism of the tetrazole-U-4CR.

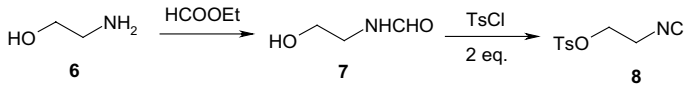


**Scheme 2.** Proposed reaction mechanism for the novel U-5C-4CR.

**Table 1.** Synthesized tetrazolopiperazines



| Entry | $R_1$ | $R_2$ | Yield (%) | Product |
|---|---|---|---|---|
| 1 | $CH_2Ph$ | $CH(CH_3)_2$ | 49 | **5a** |
| 2 | *p*-$MeOOCC_6H_4$ | $CH(CH_3)_2$ | 73 | **5b** |
| 3 | $CH_2Ph$ | *p*-$MeOC_6H_4$ | 42 | **5c** |
| 4 | $CH_2Ph$ | *p*-$MeOOCC_6H_4$ | 48 | **5d** |
| 5 | $CH_2Ph$ | *p*-$BocNHC_6H_4$ | 49 | **5e** |
| 6 | *o*-$MeOOCC_6H_4$ | $CH(CH_3)_2$ | 75 | **5f** |
| 7 | $CH_2CH(OCH_3)_2$ | Ph | 50 | **5g** |
| 8 | *o*-$MeOOCC_6H_4$ | *p*-$MeOC_6H_4$ | 56 | **5h** |
| 9 | $CH_2CH(OCH_3)_2$ | *p*-$MeOOCC_6H_4$ | 67 | **5i** |



**Scheme 3.** Two-step synthesis of 2-isocyanoethyltosylate.

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17. Typical procedure: The aldehyde (3 mmol) and the amine (3 mmol) are stirred in 10 mL methanol at room temperature. The imine is pre-condensated for 3 h and than 2 mmol of isocyanide and 2 mmol of $TMSN_3$ are added. The reaction mixture is stirred for 24 h at room temperature until the reaction is completed (indication by TLC). When the reaction is completed the solvent is evaporated and the resulting residue is dissolved in 20 mL dichloromethane. The organic layer is washed with satd $NaHCO_3$ solution and satd NaCl solution, dried over $MgSO_4$ and concentrated in vacuo. The resulting oil is purified by column chromatography on silica gel (hexane/ethyl acetate).
18. Compound **5a** was isolated in 49% yield as a white solid. $^1$H NMR ($CDCl_3$, 360.13 MHz): 0.96 (d, $^3$J = 6.8 Hz, 3H, $CH_3$), 1.20 (d, $^3J$ = 6.8 Hz, 3H, $CH_3$), 2.17 (m, 1H, C*H*Me$_2$), 2.96–3.02 (m, 1H, C$H_2$CH$_2$NRNR), 3.30–3.38 (m, 1H, C$H_2$CH$_2$NRNR), 3.64 (d, $^2J$ = 13.5 Hz, 1H, $C_6H_5CH_2$), 3.83 (d, $^2J$ = 13.5 Hz, 1H, $C_6H_5CH_2$), 3.74 (d, $^3J$ = 6.8 Hz, 1H, C*H*CHMe$_2$), 4.26–4.32 (m, 1H, CH$_2$C$H_2$NRNR), 4.42–4.50 (m, 1H, CH$_2$C$H_2$NRNR), 7.28–7.35 (m, 5H, $C_6H_5$).$^{13}$C NMR ($CDCl_3$, 90.56 MHz): 18.4 ($CH_3$), 19.8 ($CH_3$), 31.1 (*C*HMe$_2$), 42.4 (CH$_2$*C*H$_2$NRNR), 43.5 (*C*H$_2$CH$_2$NRNR), 57.8 ($C_6H_5CH_2$), 62.3 (*C*HCHMe$_2$), 127.7, 128.5, 128.7, 137.3 ($C_6H_5$), 152.2 (R$_2$C=NR). MS (ESI): *m*/*z* = 258.1 [M+H]$^+$, 280.1 [M+Na]$^+$.
Compound **5b** was isolated in 73% yield as a white solid. $^1$H NMR ($CDCl_3$, 250.13 MHz): 0.90 (d, $^3J$ = 6.71 Hz, 3H, $CH_3$), 1.05 (d, $^3J$ = 6.71 Hz, 3H, $CH_3$), 2.29–2.37 (m, 1H, C*H*Me$_2$), 3.85 (s, 3H, $COOCH_3$), 4.32–4.37 (m, 2H, C$H_2$CH$_2$NRNR), 4.54–4.61 (m, 2H, CH$_2$C$H_2$NRNR), 4.62–4.69 (m, 1H, C*H*CHMe$_2$), 6.57 (d, $^3J$ = 8.7 Hz, 2H, $C_6H_4$), 7.77 (d, $^3J$ = 8.7 Hz, 2H, $C_6H_4$). $^{13}$C NMR ($CDCl_3$, 62.90 MHz): 18.8 ($CH_3$), 19.3 ($CH_3$), 32.9 (*C*HMe$_2$), 46.7 (CH$_2$*C*H$_2$NRNR), 51.7 ($COOCH_3$), 54.4 (*C*H$_2$CH$_2$NRNR), 66.6 (*C*HCHMe$_2$), 112.3, 120.4, 131.8, 150.0 ($C_6H_4$), 155.8 (R$_2$C=NR), 166.9 (s, *C*OOMe). MS (ESI): *m*/*z* = 302.4 [M+H]$^+$, 324.3 [M+Na]$^+$.
Compound **5c** was isolated in 42% yield as a yellow oil. $^1$H NMR ($CDCl_3$, 250.13 MHz): 3.31–3.40 (m, 2H, C$H_2$CH$_2$NRNR), 3.76 (s,3H, $OCH_3$), 3.81 (d, $^2J$ = 13.12 Hz, 1H, $C_6H_5CH_2$), 3.94 (d, $^2J$ = 13.12 Hz, 1H, $C_6H_5CH_2$), 4.39–4.55 (m, 2H, CH$_2$C$H_2$NRNR), 4.88 (s, 1H, C$H_6H_4$), 6.93 (d, $^3J$ = 8.53 Hz, 2H, $C_6H_4$), 7.40–7.62 (m, 2H, $C_6H_4$), 7.21–7.39 (m, 5H, $C_6H_5$). $^{13}$C NMR ($CDCl_3$, 62.90 MHz): 45.0 (CH$_2$*C*H$_2$NRNR), 45.9 (*C*H$_2$CH$_2$NRNR), 55.3 ($OCH_3$), 57.2 ($C_6H_5CH_2$), 62.2 (*C*HC$_6$H$_4$), 114.4, 127.7, 128.6, 128.7, 129.7, 129.9, 130.3, 137.2 ($C_6H_5$, $C_6H_4$), 154.0 (s, R$_2$C=NR). MS (ESI): *m*/*z* = 322.3 [M+H]$^+$, 344.1 [M+Na]$^+$.
Compound **5d** was isolated in 48% yield as a yellow oil. $^1$H NMR ($CDCl_3$, 250.13 MHz): 2.85–2.96 (m, 1H, C$H_2$CH$_2$NRNR), 3.33–3.41 (m, 1H, C$H_2$CH$_2$NRNR), 3.43 (d, $^2J$ = 13.42 Hz, 2H, $C_6H_5CH_2$), 3.91 (s, 3H, $CH_3$), 4.27–4.58 (m, 2H, CH$_2$C$H_2$NRNR), 5.00 (s, 1H, $C_6H_4$), 7.23–7.36 (m, 5H, $C_6$ H$_5$), 7.56 (d, $^3J$ = 8.24 Hz, 2H, $C_6H_4$), 8.07 (d, $^3J$ = 8.24 Hz, 2H, $C_6H_4$). $^{13}$C NMR ($CDCl_3$, 62.90 MHz): 44.7 (CH$_2$*C*H$_2$NRNR), 45.7 (*C*H$_2$CH$_2$NR NR), 52.1 ($CH_3$), 57.3 ($C_6H_5CH_2$), 62.0 (*C*HC$_6$H$_4$), 127.8, 128.5, 128.6, 129.8, 130.3, 130.5, 136.6, 141.9 ($C_6H_5$, $C_6H_4$), 152.7 (R$_2$C=NR), 166.4 (*C*OOMe). MS (ESI): *m*/*z* = 350.5 [M+H]$^+$, 372.3 [M+Na]$^+$.
Compound **5e** was isolated in 49% yield as a yellow solid. $^1$H NMR ($CDCl_3$, 250.13 MHz): 1.43 (s, 9H, [C(C$H_3$)$_3$], 2.70–2.81 (m, 1H, C$H_2$CH$_2$NRNR), 3.24–3.31 (m, 1H, C$H_2$CH$_2$NRNR), 3.29 (d, $^2J$ = 13.42 Hz, 1H, $C_6H_5CH_2$), 3.83 (d, $^2J$ = 13.42 Hz, 1H, $C_6H_5CH_2$), 4.15–4.45 (m, 2H, CH$_2$C$H_2$NRNR), 4.80 (s, 1H, $C_6H_4$), 6.63 (s, 1H, NH), 7.21–7.38 (m, 9H, $C_6H_5C_6H_4$). $^{13}$C NMR ($CDCl_3$, 62.90 MHz): 28.3 [C(*C*H$_3$)$_3$], 45.0 (CH$_2$*C*H$_2$NRNR), 45.8 (*C*H$_2$CH$_2$NRNR), 57.2 ($C_6H_5CH_2$), 62.1 (*C*HC$_6$H$_4$), 80.7 [*C*(CH$_3$)$_3$], 118.9, 127.7, 128.6, 128.7, 129.2, 130.0, 137.1, 139.0 ($C_6H_5$, $C_6H_4$), 152.6 (R$_2$C=NR), 153.5 (COOR). MS (ESI): *m*/*z* = 407.2 [M+H]$^+$, 429.1 [M+Na]$^+$.
Compound **5f** was isolated in 75% yield as a white solid. $^1$H NMR ($CDCl_3$, 250.13 MHz): 0.94 (d, $^3J$ = 6.72 Hz, 3H, $CH_3$), 1.18 (d, $^3J$ = 6.72 Hz, 3H, $CH_3$), 2.36 (m, 1H, C*H*Me$_2$), 3.91 (s, 3H, $COOCH_3$), 4.28–4.42 (m, 2H, C$H_2$ CH$_2$NRNR), 4.51–4.70 (m, 2H, CH$_2$C$H_2$NRNR), 4.80 (t, $^3J$ = 6.72 Hz, 1H, C*H*CHMe$_2$), 6.53 (d, $^3J$ = 8.54 Hz, 1H, $C_6H_4$), 6.65–6.72 ($C_6H_4$), 7.93–7.97 [m, 1H ($C_6H_4$)], 8.37 (d, $^3J$ = 5.8 Hz, 1H, $C_6H_4$). $^{13}$C NMR ($CDCl_3$, 62.90 MHz): 19.3 ($CH_3$), 19.5 ($CH_3$), 33.0 (*C*HMe$_2$), 46.6 (CH$_2$*C*H$_2$NRNR), 51.8 (COO*C*H$_3$), 55.2 (*C*H$_2$CH$_2$ NRNR), 66.2 (*C*HCHMe$_2$), 111.1, 111.5, 116.7, 131.9, 135.1, 149.2 ($C_6H_4$), 155.7 (R$_2$C=NR), 169.2 (*C*OOMe). MS (ESI): *m*/*z* = 302.3 [M+H]$^+$, 324.2 [M+Na]$^+$.
Compound **5g** was isolated in 50% yield as a yellow oil. $^1$H NMR ($CDCl_3$, 250.13 MHz): 2.62–2.81 [m, 2H, (MeO)$_2$CHC$H_2$], 3.05–3.15 (m, 1H, C$H_2$CH$_2$NRNR), 3.58–3.67 (m, 1H, C$H_2$CH$_2$NRNR), 3.21 (s, 3H, $OCH_3$), 3.36 (s, 3H, $OCH_3$), 4.38–4.43 [m, 1H, (MeO)$_2$C*H*], 4.47–4.59 (m, 2H, CH$_2$C$H_2$NRNR), 5.07 (s, 1H, $C_6H_5$), 7.26–7.40 (m, 5H, $C_6H_5$). $^{13}$CNMR ($CDCl_3$, 62.90 MHz): 44.8 (CH$_2$*C*H$_2$NRNR), 47.2 (*C*H$_2$CH$_2$NRNR), 53.4 ($OCH_3$), 54.0 (s, $OCH_3$), 54.6 [(MeO)$_2$CH*C*H$_2$], 62.5 (*C*HC$_6$H$_5$), 104.0 [(MeO)$_2$*C*H], 128.6, 128.8, 128.9, 136.8 ($C_6H_5$), 153.3 (R$_2$C=NR). MS (ESI): *m*/*z*=290.3 [M+H]$^+$, 312.2 [M+Na]$^+$.
Compound **5h** was isolated in 56% yield as a yellow oil. $^1$H NMR ($CDCl_3$, 250.13 MHz): 3.72 (s, 3H, $OCH_3$), 3.82 (s, 3H, $COOCH_3$), 4.22 (t, $^3J$ = 5.19 Hz, 2H, C$H_2$CH$_2$ NRNR), 4.42 (t, $^3J$ = 5.19 Hz, 2H, CH$_2$C$H_2$NRNR), 6.09 (d, 1H, $C_6H_4$), 6.83 (d, $^3J$ = 8.54 Hz, 2H, $C_6H_4$OMe), 7.46 (d, $^3J$ = 8.54 Hz, 2H, $C_6H_4$OMe), 7.19–7.28 (m, 4H, $C_6H_4$COOMe). $^{13}$C NMR ($CDCl_3$, 62.90 MHz): 46.4 (CH$_2$*C*H$_2$ NRNR), 51.7 (*C*H$_2$CH$_2$NRNR), 51.8 (COO *C*H$_3$), 55.3 ($OCH_3$), 66.3 (*C*HC$_6$H$_4$), 111.7, 112.0, 114.9, 116.9, 130.0, 131.6, 131.8, 134.9, 148.5, 160.0 ($C_6H_4$CO-OMe, *C*$_6$H$_4$OMe), 156.0 (R$_2$C=NR), 169.0 (*C*OOMe). MS (ESI): *m*/*z* = 366.5 [M+H]$^+$, 388.4 [M+Na]$^+$.

Compound **5i** was isolated in 67% yield as a yellow oil. $^{1}$H NMR ($CDCl_3$, 250.13 MHz): 2.72 [m, 2H, $(MeO)_2CH$ $CH_2$], 3.09–3.19 (m, 2H, $CH_2CH_2NRNR$), 3.23 (s, 3H, $OCH_3$), 3.36 (s, 3H, $OCH_3$), 3.92 (s, 3H, $COOCH_3$), 4.38–4.46 [m, 1H, $(MeO)_2CH$], 4.48–4.60 (m, 2H, $CH_2CH_2$ NRNR), 5.18 (s, 1H, $C_6H_4$), 7.47 (d, $^{3}J = 8.39$ Hz, 2H, $C_6H_4$), 8.05 (d, $^{3}J = 8.39$ Hz, 2H, $C_6H_4$). $^{13}$C NMR ($CDCl_3$, 62.90 MHz): 44.7 ($CH_2CH_2NRNR$), 47.2 ($C_2CH_2NRNR$), 52.2 ($COOCH_3$), 53.6 [$(MeO)_2CHCH_2$], 54.1 ($OCH_3$), 54.6 ($OCH_3$), 61.94 ($CHC_6H_4$), 103.8 [$(MeO)_2CH$], 128.6, 130.1, 130.2, 141.9($C_6H_4$), 152.6 ($R_2C{=}NR$), 166.5 ($COOMe$). MS (ESI): $m/z = 348.4$ $[M+H]^+$, 370.1 $[M,+Na]^+$.

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