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A new and versatile Ugi/S_NAr synthesis of fused 4,5-dihydrotetrazolo[1,5-*a*]quinoxalines

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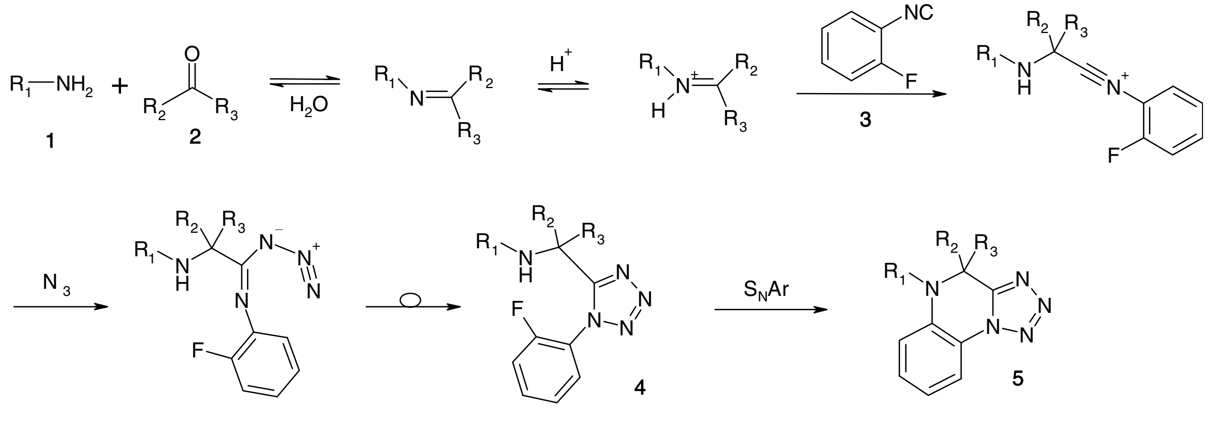
Abstract—A combinatorial synthetic route yielding fused tetrazolo[1,5-*a*]quinoxalines is described. The use of 2-fluorophenylisocyanide in the Ugi-tetrazole reaction (tetrazole-U-4CR) followed by a nucleophilic aromatic substitution (S_NAr) affords the tricylic tetrazolo[1,5-*a*]quinoxaline moiety in good yields and with high diversity.

Synthetic sequences that enable the parallel automated synthesis of polysubstituted heterocycles have attracted considerable attention in recent years.[1,2] Robust synthesis of 'drug-like' compounds permits the fast preparation of compound libraries suitable for lead discovery and optimization.[3,4] Therefore, the easily automated multi-component reactions (MCRs) are powerful tools for this high-throughput screening strategy.[5,6]

One of the most reported multi-component reactions is the Ugi-reaction.[7] The four-component reaction (U-4CR) between amine, aldehyde, carboxylic acid and isocyanide affords peptidic structures in high diversity. In the last years, many research groups extended the potential of the U-4CR by using bi-functional starting materials.[8–11] Hulme and co-workers combined the U-4CR with different post-condensation reactions to produce a large range of biologically relevant heterocycles.[12–15] For example, the combination of the Ugi-reaction with a post-condensation(S_NAr) generates indazolinones, benzazepines and benzoxazepines[16,17] or product-like biaryl ether containing macrocycles.[18–20]



Scheme 1. Two-step combinatorial synthesis of 4,5-dihydrotetrazolo[1,5-*a*]quinoxalines.

Keywords: Ugi-reaction; Multi-component reaction; Tetrazole; Fused tetrazoloquinoxaline; Nucleophilic aromatic substitution.

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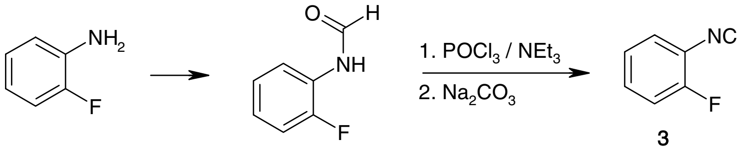

Scheme 2. Synthesis of the 2-fluorophenylisocyanide.

Following this strategy, we report a new and versatile two-step solution-phase synthesis of fused tetrazolo[1,5-*a*]quinoxalines. The first step of this synthesis consists in a classical Ugi-tetrazole reaction[21,22] yielding bis-substituted tetrazoles (Scheme 1). We involved 2-fluorophenylisocyanide **3** as a new bifunctional starting material in this multi-component synthesis to enable a subsequent nucleophilic aromatic substitution (S_NAr).

2-Fluorophenylisocyanide **3** is obtained in two steps by formylation of the commercially available amine followed by dehydration using phosphoroxychloride[23] (Scheme 2).

The Ugi-tetrazole synthesis is a variation of the classical Ugi-reaction where azidotrimethylsilane ($TMSN_3$) is employed as acid component. This reaction is initiated by condensation of an aldehyde or ketone **2** with an amine **1**. Subsequent reaction with isocyanide produces the intermediate nitrilium ion, as a key intermediate. The desired tetrazole is obtained by reaction with the azide, followed by sigmatropic rearrangement. Experimentally, we used to mix the four components amine/aldehyde/$TMSN_3$/**3** in a ratio 1/1/1.5/1.5 to obtain the best yields.[24] Under these conditions, a two-step one-pot synthesis could not be envisaged because an excess of compound **3** would be a source of secondary reactions during the subsequent nucleophilic aromatic substitution. Therefore, the resulting tetrazoles were purified by crystallization or chromatographic methods before they were involved in the second step of the U-4CR/S_NAr synthetic strategy. The synthesized tetrazoles **4a**–**i** are shown in Table 2. They were obtained in good yields (Y_1) and with general high purity (>95%).

Afterwards, the tetrazoles have to be treated with a base to afford the desired post-condensation (S_NAr). Different experiments have been realized with tetrazole **4a** in different solvents and bases to optimize the reaction conditions (Table 1). Conversions (Y) were evaluated by HPLC-MS after 3 h of reaction time. Results prove that cesium carbonate in combination with a reaction temperature of 100 °C seems to be the ideal base.

Thus, all S_NAr-reactions were performed under these conditions.[25] Results and synthesized fused 4,5-dihydrotetrazolo[1,5-*a*]quinoxalines **5a**–**i** are reported in Table 2 with specific yields (Y_2).

The reaction times (rt) for the S_NAr are generally short, and the conversion is excellent for all compounds. Chromatography methods allow the obtention of products with high purity (>95%). The reaction is very convenient and does not affect the versatility of the starting materials.

Table 1. S_NAr optimization

Ex	Base	Equivalent	Solvent	T (°C)	Y (%)
1	$NaHCO_3$	1.3	MeOH	80	1
2	Cs_2CO_3	1.3	DMF	25	2
3	Cs_2CO_3	1.3	DMF	100	96

In summary, a novel two-step solution phase procedure for the preparation of highly substituted 4,5-dihydrotetrazolo[1,5-*a*]quinoxalines has been described. Amines and carbonyles can be varied broadly, yielding tricyclic tetrazoles with three potential diversity points. Therefore, an access to thousands of diverse analogues with the aforementioned core structure is now feasible. At least, the use of some bifunctional starting materials could enable further extension of the tetrazolo[1,5-*a*]quinoxaline moiety.

Current efforts are now focusing on the use of this reaction for the development of new pharmacological scaffolds.

References and notes

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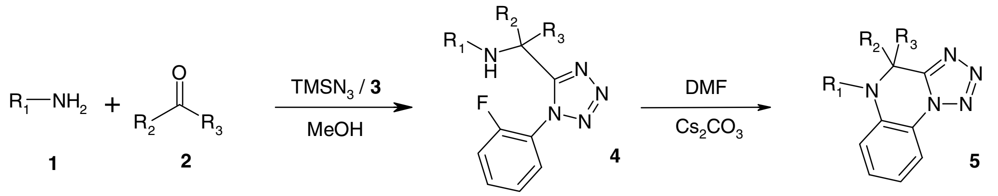
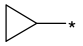
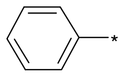
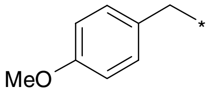
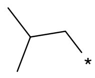
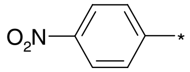
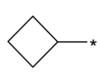
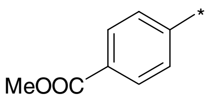
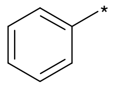
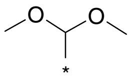
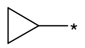
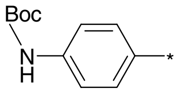
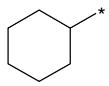
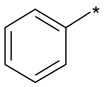
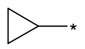
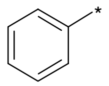
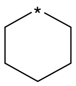
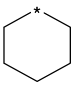
Table 2. Synthesized fused 4,5-dihydrotetrazolo[1,5-*a*]quinoxalines



Entry	R_1	R_2	R_3	Y_1 (%)	Product	Reaction time (h)	Y_2 (%)	Product
1			H	62	**4a**[26]	3[a]	96	**5a**[27]
2		C_2H_5	H	17	**4b**	3[a]	95	**5b**
3			H	29	**4c**	3[a]	95	**5c**
4			H	61	**4d**	3[a]	92	**5d**
5			H	58	**4e**	3[a]	95	**5e**
6			H	46	**4f**	15[b]	94	**5f**
7			H	65	**4h**	10[c]	74	**5g**
8		CH_3	CH_3	52	**4g**	48[b]	57	**5h**[28]
9				44	**4i**	10[c]	96	**5i**[29]

[a] 1.3 equiv Cs_2CO_3.

[b] 2.3 equiv Cs_2CO_3.

[c] 1.8 equiv Cs_2CO_3.

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23. 2-Fluorophenylisocyanide **3**: 5.55 g (50 mmol) of **2** was dissolved in 50 mL methylene chloride. Triethylamine (12.14 g) was added and the mixture was cooled to 0 °C. Phosphoroxychloride (7.66 g/50 mmol) was added dropwise to the reaction mixture between 0 °C and 5 °C. The mixture was then stirred for 1 h by room temperature. Then, 10 g (94 mmol) sodium carbonate in 40 mL water was added dropwise. The precipitate was removed by filtration, and the organic layer was washed two times with 30 mL brine, dried over potassium carbonate and evaporated under vacuum. Distillation by 11 mbar (bp = 47 °C) afforded 2.52 g (20 mmol) of compound **3** as a green oil. ^{1}H NMR ($CDCl_3$, 250.13 Hz): 7.16–7.21 (m, 2H, aryl), 7.37–7.43 (m, 2H, ar-H). ^{13}C NMR ($CDCl_3$, 62.89 MHz): 116.66 (d, $^2J_{(C–F)} = 18.38$ MHz, C3), 124.68 (d, $^4J_{(C–F)} = 3.68$ Hz, C5), 128.01 (s, C6), 130.95 (d, $^3J_{(C–F)} = 7.36$ Hz, C4), 155.42 (s, C1), 159.51 (s, C2), 170.19 (N*C*).
24. General procedure (GP1) for the synthesis of tetrazoles **4a**–**i**: amine **1** (3 mmol) and carbonyle **2** (3 mmol) were stirred in 3 mL MeOH for 2 h. Then, azidotrimethylsilane $TMSN_3$ (3.8 mmol) and isocyanide **3** (3.8 mmol) was added and the reaction mixture was stirred for 48 h. After evaporation of the solvent, 15 mL methylene chloride was added and the organic layer was washed with 2 × 10 mL

brine, dried over $MgSO_4$ and the solvent was removed. The obtained 1,5-disubstituted tetrazole **4** was purified by chromatographic methods or crystallization.

25. General procedure (GP2) for the synthesis of 4,5-dihydrotetrazolo[1,5-*a*]quinoxalines **5a**–**i**: 0.2 mmol of compound **4** was dissolved in 2 mL DMF and 0.33 mmol Cs_2CO_3 was added. Then, the reaction was stirred until HPLC–MS analysis confirmed that the reaction was completed. Then, 10 mL water were added and the mixture was extracted with 2 × 15 mL of ethyl acetate. The organic layer was dried over $MgSO_4$ and the resulting crude product was purified by flash chromatography.
26. Compound **4a** was prepared according to GP1 and purified by chromatography on silica gel with eluent ethyl acetate/hexane 2/1. The tetrazole **4a** was obtained as a yellow oil (62%). ^1H NMR ($CDCl_3$, 250.13 MHz): 0.35 (s, 4H, CH_2), 2.07 (t, 1H, $^3J = 4.17$ MHz, C*H* cyclopropyl), 2.83 (s, 1H, N*H*), 4.99 (s, 1H, C*H*-C_6H_5), 7.1–7.32 (m, 8H, ar-H), 7.52–7.61 (m, 1H, ar-H). *m*/*z* (%) = 310 (100) [MH+].
27. Compound **5a** was prepared according to GP2 and purified by chromatography on silica gel with eluent ethyl acetate/hexane 1/2 to afford **5a** (mixture of two conformers in a ratio 1/0.85) as a yellow oil (96%). ^1H NMR of major isomer ($CDCl_3$, 250.13 MHz): 0.80–0.90 (m, 4H, CH_2), 2.62–2.70 (m, 1H, C*H*), 7.15–7.48 (m, 10H, ar-H and C*H*–C_6H_5). *m*/*z* (%) = 290 (100) [MH+].
28. Compound **5h** was prepared according to GP2: 258 mg (1 mmol) of **4h** was dissolved in 6 mL DMF and 586 mg (1.8 mmol) Cs_2CO_3 was added. Then, the reaction was stirred for 1 d at 100 °C. Then, 163 mg (0.5 mmol) Cs_2CO_3 were added and the mixture was stirred for a following 24 h. Despite the reaction was not being completed, 15 mL water was added and the mixture was extracted with 2 × 25 mL of ethyl acetate. The organic layer was dried over $MgSO_4$ and the resulting crude product was purified on silica gel with eluent ethyl acetate/hexane 1/2 to afford **5h** as a colourless oil (135 mg/57%). ^1H NMR ($CDCl_3$, 250.13 MHz): 0.60–0.67 (m, 2H, CH_2), 1.01–1.09 (m, 2H, CH_2), 1.73 (s, 6H, C–$(CH_3)_2$), 2.36–2.42 (m, 1H, C*H*), 7.02–7.09 (m, 1H, ar-H), 7.34–7.40 (m, 2H, ar-H), 7.89–7.92 (dd, 1H, $^3J = 6.95$ Hz, $^4J = 1.42$ Hz, ar-H). ^{13}C NMR ($CDCl_3$, 62.89 MHz): 10.10 (CH_2), 22.96 (C–$(CH_3)_2$), 25.00 (*C*H), 57.51 (*C*–$(CH_3)_2$), 116.85, 117.75, 120.36, 122.05, 129.02, 137.08 (ar), 154.72 ($R_2C{=}NR$). *m*/*z* (%) = 242 (100) [MH+].
29. Compound **5i** was prepared according to GP2: 221 mg (0.7 mmol) of **4i** was dissolved in 5 mL DMF and 586 mg (1.8 mmol) Cs_2CO_3 was added. Then, the reaction was stirred for 10 h by 100 °C. After HPLC–MS analysis which confirmed that the reaction was completed, 15 mL water was added and the mixture was extracted with 2 × 20 mL of ethyl acetate. The organic layer was dried over $MgSO_4$ and the resulting crude product was purified on silica gel with eluent ethyl acetate/hexane 1/3 to afford **5i** as a white solid. Mp: 138.3–138.5 °C. ^1H NMR ($CDCl_3$, 250.13 MHz): 1.61–1.76 (m, 6H, cyclohexyl), 1.89–2.08 (m, 2H, cyclohexyl), 2.15–2.20 (m, 2H, cyclohexyl), 6.35 (dd, 1H, $^3J = 8.37$ Hz, $^4J = 0.95$ Hz, ar-H), 6.93 (ddd, 1H, $^3J_a = 7.82$ Hz, $^3J_b = 8.69$ Hz, $^4J = 1.11$ Hz, ar-H), 7.08 (dt, 1H, $^3J = 8.69$ Hz, $^4J = 1.58$ Hz, ar-H), 7.21–7.26 (m, 2H, ar-H), 7.44–7.51 (m, 3H, ar-H), 7.99 (dd, 1H, $^3J = 7.82$ Hz, $^4J = 1.58$ Hz, ar-H). ^{13}C NMR ($CDCl_3$, 62.89 MHz): 22.35 (cyclohexyl), 24.98 (cyclohexyl), 34.44 (cyclohexyl), 60.16 (*C*q), 117.10, 117.58, 119.31, 120.75, 128.48, 129.16, 129.97, 131.96, 136.57, 140.20 (ar), 151.82 ($R_2C{=}NR$). *m*/*z* (%) = 318 (100) [MH+].