tert-Butyl Isocyanide as a Convertible Reagent in Ugi Reaction: Microwave-Assisted Preparation of 5,6-Dihydropyrazolo[1,5-*a*]pyrazine-4,7-diones

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Abstract: *tert*-Butyl amides resulting from Ugi MCR of *t*-BuNC and 5-substituted-1*H*-pyrazole-3-carboxylic acids with various aldehydes and amines undergo cyclization into 5,6-dihydropyrazolo[1,5-*a*]pyrazine-4,7-diones in glacial acetic acid under microwave irradiation. This reaction is a remarkable case of neighboring-group-assisted cleavage of *tert*-butyl amides and demonstrates utility of *t*-BuNC as a new convertible isocyanide.

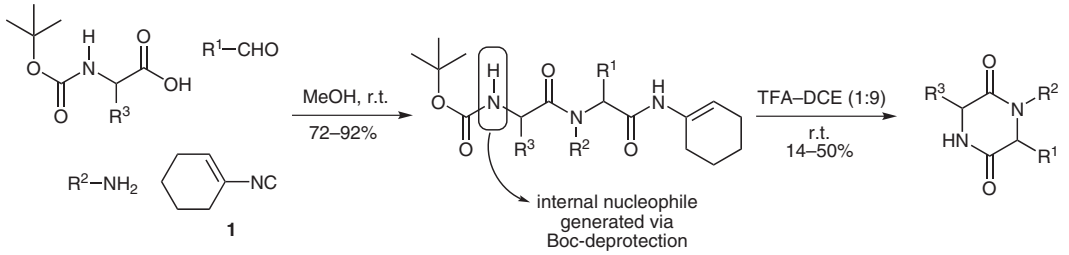
Key words: Ugi multicomponent reaction, convertible isocyanides, microwave-assisted cyclization, post-Ugi MCR cyclization

While designing reaction arrays based on the Ugi multicomponent reaction (Ugi MCR),[1] it is often desirable not to rely on the isocyanide component as the source of product diversity and rather take advantage of this efficient process to unite the other three reaction components with a single convertible isocyanide. The resulting Ugi reaction products are then suitable for use as substrates for selective post-MCR modification of the former isocyanide portion. Notably, such modifications can involve an 'internal nucleophile' and result in a cyclization process, as exemplified by preparation of diketopiperazine library described by Hulme and co-workers[2] (Scheme 1).

In order to qualify as convertible, an isocyanide should be designed so as to allow selective cleavage of the respective amide in the Ugi reaction product without affecting the other amide moiety present in the same product. Convertible isocyanides reported to date include notable examples of cyclohex-1-enyl isocyanide (**1**, 'Armstrong's isonitrile'),[3] 2-isocyano-2-methylpropyl carbonates,[4] and recently reported 1-isocyano-2-(2,2-dimethoxyethyl)benzene (termed as 'indole isonitrile').[5] 1,1,3,3-Tetramethylbutyl isocyanide ('Walborsky reagent'[6]) has been successfully employed[7] in isocyanide-based multicomponent reactions with subsequent conversion of the isooctylamino moiety into a primary amino group potentially suitable for functionalization.

In our ongoing research, we aim at developing efficient approaches to combinatorial libraries based on medicinally relevant scaffolds. Our recent interest was attracted by 5,6-dihydropyrazolo[1,5-*a*]pyrazine-4,7-diones **2**. This drug-like core fragment has a strong potential for identifying various biological activities, as witnessed by several antibacterial,[8] anti-inflammatory,[9] antitumor,[10] and CNS-active[11] compounds reported in the literature. However, rapid approaches to generating vast arrays of such compounds with controlled diversity have not been described. This, and also the opportunity to explore a post-MCR condensation strategy (not dissimilar to that described for diketopiperazinones – vide supra) as a novel way to prepare **2** (Scheme 2) constituted the premise for this study.

An important aspect that we considered before preparation of the Ugi reaction products as precursors to the target 5,6-dihydropyrazolo[1,5-*a*]pyrazine-4,7-diones **2** was the choice of an appropriate convertible isocyanide. Although the Armstrong's isocyanide was demonstrated to be the reagent of choice to prepare Ugi-type substrates for post-MCR cyclizations (and superior to benzyl, *n*-butyl, cyclohexyl, isopropyl isocyanides, and Walborsky reagent),[2] it has obvious disadvantages.



Scheme 1 Post-MCR cyclization leading to diketopiperazines[2]

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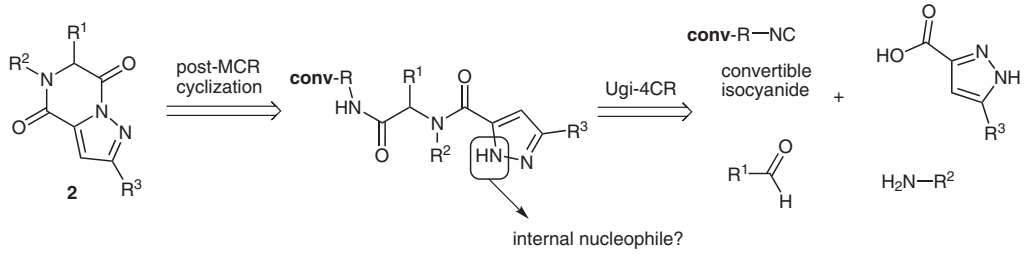
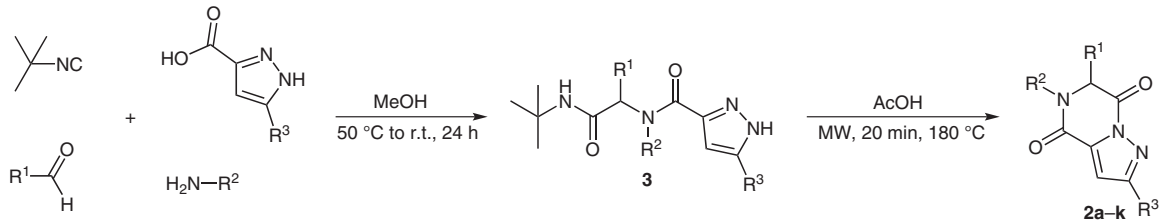


Scheme 2 5,6-Dihydropyrazolo[1,5-*a*]pyrazine-4,7-diones **2** via post-MCR cyclization?

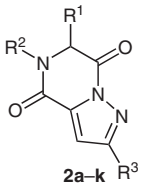


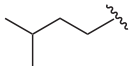
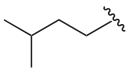
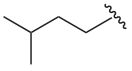
Scheme 3 Synthesis of quinoxalines **5a**–**h** via intermediate formation of 1,4-dihydroquinoxalines **4a**–**h**

It is commercially unavailable, has limited stability, requires freezer storage, and cannot be prepared on a large scale.[12] Herein we report that for preparation of 5,6-dihydropyrazolo[1,5-*a*]pyrazine-4,7-diones **2**, the Armstrong's isocyanide can be replaced with readily available *tert*-butyl isocyanide and the desired post-MCR cyclization of **3** is efficiently promoted by microwave irradiation in glacial acetic acid (Scheme 3).[13]

The two-step procedure to prepare **2** was designed so as to allow carrying out both steps in the same reaction vessel (microwave reactor tube) and thus be amenable for preparation of large arrays of the final compounds in parallel format. To prepare each of the bisamides **3**, equimolar amounts of an aldehyde and amine were combined in methanol (0.5 mmol each/1 mL MeOH) and heated at 50 °C for two hours to ensure complete imine formation. Then a solution of a 1*H*-pyrazole-3-carboxylic acid (0.5 mmol) in methanol (1 mL) was added followed, after five minutes of stirring, by a solution of *t*-BuNC (0.5 mmol) in methanol (1 mL). Then the mixtures were left under stirring at room temperature for 24 hours. The solvent was removed in vacuo[14] and the resulting products were shown to be at least 85% pure by LC-MS analysis in all cases.[15] Without further purification, these were dissolved in glacial AcOH (3 mL each) and the reaction vessels were capped. After heating the reaction mixtures at 180 °C under microwave irradiation for 20 minutes (using Biotage Initiator™ microwave synthesizer operating at 100 W), these were poured into water (25 mL), and the resulting thick precipitates were collected by filtration. In all cases, the resulting products were isolated in at least 90% purity, and their molecular weight was indicative of a loss of a *tert*-butylamino group, as determined by LC-MS (Scheme 2). Further purification of the products by column chromatography on silica (gradients of ethyl acetate in hexanes) afforded analytically pure products in fair to good yields over two steps (Table 1). The identity of the products was confirmed as 5,6-dihydropyrazolo[1,5-*a*]pyrazine-4,7-diones **2** by ^{1}H NMR and ^{13}C NMR spectroscopy as well as elemental analyses.[16]

Table 1 5,6-Dihydropyrazolo[1,5-*a*]pyrazine-4,7-diones **2** Prepared in this Work



Entry	**2**	R^1	R^2	R^3	Yield (%)
1	**2a**	4-$EtOC_6H_4$	Ph	2-MeC_6H_4	61
2	**2b**	4-$EtOC_6H_4$	4-$MeOC_6H_4CH_2$	4-FC_6H_4	65
3	**2c**	4-$EtOC_6H_4$	4-$MeOC_6H_4CH_2$	3-MeC_6H_4	56
4	**2d**	4-$EtOC_6H_4$	4-$MeOC_6H_4CH_2$	2-MeC_6H_4	42
5	**2e**	4-$EtOC_6H_4$		2-MeC_6H_4	43
6	**2f**	3-$MeOC_6H_4$	4-$MeOC_6H_4CH_2$	2-MeC_6H_4	45
7	**2g**	3-$MeOC_6H_4$		4-FC_6H_4	38
8	**2h**		Ph	4-FC_6H_4	67
9	**2i**		4-$MeOC_6H_4CH_2$	4-FC_6H_4	52
10	**2j**		Ph	4-FC_6H_4	70
11	**2k**			4-FC_6H_4	46

In conclusion, we developed a streamlined two-step, one-purification approach to medicinally important 5,6-dihydropyrazolo[1,5-*a*]pyrazine-4,7-diones using an Ugi 4CR–post-MCR cyclization approach. We demonstrated for the first time that in the microwave-assisted cyclization process, the readily available *tert*-butyl isocyanide can function as convertible isocyanide thus offering a more convenient and economical alternative to previously used Armstrong's isocyanide. We are now investigating if other isocyanides and azole carboxylic acids can be incorporated via Ugi reaction into precursors for post-MCR cyclization. The results of these studies will be reported in due course.

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(13) Other reaction conditions that were screened and proved inefficient for post-MCR cyclization of **3** included conventional heating in AcOH, conventional and microwave heating in TFA, as well as using base promoters (KO*t*-Bu, NaH) in various solvents (e.g., THF, DMF, dioxane). *tert*-Butyl isonitrile was chosen on the basis of its commercial availability in large quantities. However, we are also finding it superior to other isocyanides in the present post-MCR cyclization. These finding will be disclosed in a separate communication.
(14) Parallel evaporation of volatiles from the microwave reactor tube was carried out using GeneVac® equipment.
(15) No further purification and characterization (except LC-MS analysis) of the crude Ugi reaction products **3** were performed.
(16) **Characterization Data for Selected Compounds**
Compound **2f**: white solid, mp 122–123 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 (s, 1 H), 7.50–7.55 (t, *J* = 8.1 Hz, 1 H), 7.27–7.31 (m, 2 H), 7.19–7.24 (m, 1 H), 7.08–7.13 (m, 3 H), 7.00 (ddd, *J* = 8.4, 2.5, 1.0 Hz, 1 H), 6.89 (d, *J* = 8.4 Hz, 2 H), 5.63 (d, *J* = 14.5 Hz, 1 H), 5.58 (s, 1 H), 3.87 (s, 3 H), 3.82 (s, 3 H), 3.45 (d, *J* = 14.5 Hz, 1 H), 2.38 (s, 3 H). ^{13}C NMR (75Hz, $CDCl_3$): δ = 160.2, 159.7, 159.3, 158.1, 154.3, 138.0, 137.3, 132.1, 131.5, 131.1, 129.8, 129.5, 129.1, 126.6, 126.3, 125.7, 119.1, 116.4, 114.1, 111.1, 110.4, 60.6, 55.0, 54.9, 45.6, 19.2. LC-MS: *m/z* = 433 [M + H]. Anal. Calcd for $C_{28}H_{25}N_3O_4$: C, 71.93; H, 5.39; N, 8.99. Found: C, 72.04; H, 5.43; N, 9.02.
Compound **2i**: beige solid, mp 152–153 °C (decomp.). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 (dd, *J* = 7.4, 5.3 Hz, 2 H), 7.07–7.12 (m, 4 H), 6.83–6.90 (m, 3 H), 5.57 (d, *J* = 14.5 Hz, 1 H), 5.17 (s, 1 H), 3.79 (s, 3 H), 3.48 (d, *J* = 14.5 Hz, 1 H), 2.03–2.12 (m, 1 H), 1.05–1.15 (m, 2 H), 0.90–0.96 (m, 2 H). ^{13}C NMR (75Hz, $CDCl_3$): δ = 164.0, 162.9 (d, J_{C-F} = 248.5 Hz), 159.5, 159.3, 153.9, 137.2, 129.7, 129.5 (d, J_{C-F} = 2.9 Hz), 128.7 (d, J_{C-F} = 8.6 Hz), 126.1, 116.3 (d, J_{C-F} = 21.7), 114.1, 110.4, 63.3, 54.4, 45.5, 9.2, 9.1, 8.9. LC-MS: *m/z* = 406 [M + H]. Anal. Calcd for $C_{23}H_{20}FN_3O_3$: C, 68.14; H, 4.97; N, 10.36. Found: C, 68.19; H, 5.03; N, 10.39.
Compound **2j**: white solid, mp 147–149 °C (decomp.). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 3.5 Hz, 1 H), 7.48 (s, 1 H), 7.46 (d, *J* = 5.0 Hz, 1 H), 7.25–7.37 (m, 5 H), 7.12–7.18 (m, 3 H), 7.02 (t, *J* = 8.4 Hz, 2 H), 5.76 (s, 1 H). ^{13}C NMR (75Hz, $CDCl_3$): δ = 162.9 (d, J_{C-F} = 248.5 Hz), 159.6, 153.7, 153.4, 138.1, 137.5, 132.4, 130.2 (d, J_{C-F} = 2.8 Hz), 129.1, 128.7 (d, J_{C-F} = 8.6 Hz), 129.3, 128.0, 127.9, 127.6, 126.7, 116.1 (d, J_{C-F} = 22.1), 111.0, 68.7. LC-MS: *m/z* = 404 [M + H]. Anal. Calcd for $C_{22}H_{14}FN_3O_2S$: C, 65.50; H, 3.50; N, 10.47. Found: C, 65.54; H, 3.60; N, 10.51.