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A new approach to four- and five-component Ugi condensations starting from nitriles

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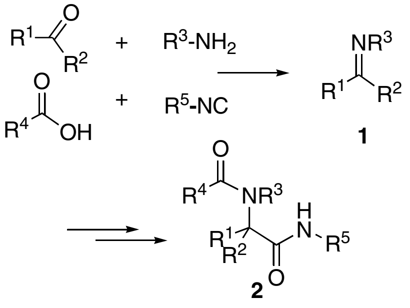
Abstract—New four- and five-component Ugi condensations have been developed based on the reaction of organometallic reagents with nitriles. These variations expand both the range of inputs and overall dimensionality of the method.

Ugi's seminal report in 1961[1] of the in situ condensation of isonitriles, carboxylic acids and amines with aldehydes or ketones to form α-aminoacid diamides defined one of the most widely used multiple component condensation (MCC) reactions in organic synthesis (Scheme 1). Since its discovery, the Ugi reaction remains one of the few MCC processes capable of generating pharmaceutically relevant molecular complexity in a single step.

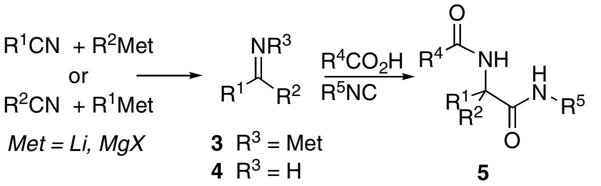
While several variations and combinations of the four basic components have been explored,[2] relatively few examples of ketone-derived Ugi products have been reported. Moreover, little work has been done to broaden the types of available inputs leading to the product α-aminoacid diamides **2**. As part of our interest in expanding the repertoire of MCC reactions,[3] we have found that Ugi products can be prepared from a different set of reactants. That set affords an alternative approach to the key imine intermediate **1**. Here, we report four-component condensations of nitriles, organometallic reagents, carboxylic acids and isonitriles as well as higher order, five-component variations that furnish Ugi products in good yield.



Scheme 1.

We reasoned that protonation of metallated ketimines **3** (Scheme 2), which can be generated in principle by two complementary combinations of nitriles with either Grignard[4] or organolithium[5] reagents, might provide a direct route to N-unsubstituted ketimines **4** for the synthesis of diamides **5**. Because imines like **4** are otherwise difficult to form by the usual ammonia–ketone equilibrium, Ugi reactions involving pre-formed imines are known to give substantially better yields of product.[6]

In fact, the overall transformation depicted in Scheme 2 can be successfully implemented as an alternative four-component diamide synthesis that replaces carbonyl and amine reactants used in the Ugi process with nitriles



Scheme 2.

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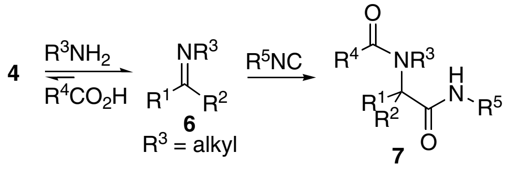
Table 1. Four-component condensations of R^1CN, R^2Met, R^4CO_2H and R^5NC leading to diamides **5**

R^1 = (1.4 equiv)	R^2Met = (1.5 equiv)	R^4 = (3.5–4.5 equiv)	R^5 = (1.0 equiv)	Product (yield)
Et	*n*-BuLi	CH_3	Cyclohexyl	**5a** (70%)
Et	*n*-BuLi	CH_3	Morpholinoethyl	**5b** (69%)
Et	PhMgBr	CH_3	Cyclohexyl	**5c** (45%)
n-C_5H_{11}	MeLi	Ph	Cyclohexyl	**5d** (66%)
n-C_5H_{11}	MeLi	Ph	CH_2CO_2Et	**5e** (64%)
n-C_5H_{11}	*p*-MeO-C_6H_4Li	CH_3	*n*-Bu	**5f** (45%)
n-C_5H_{11}	*n*-BuMgCl	$(CH_3)_2CH$	*t*-Bu	**5g** (67%)
Cyclohexyl	*n*-BuLi	PhCH=CH	Morpholino ethyl	**5h** (68%)
Ph	*n*-BuLi	$(CH_3)_2CH$	Cyclohexyl	**5i** (41%)

and organometallic reagents. The scope and versatility is illustrated by the examples shown in Table 1.

By using anhydrous ether as solvent in the addition of organolithium reagents (or benzene for Grignard reagents)[7] byproducts arising from competing deprotonation reactions of α-acidic nitriles[8] could be suppressed so as to obtain metallated ketimines **3** in good yield. Protonation of **3** was achieved by the addition of CH_3OH (a preferred solvent for Ugi condensations). The reaction mixture was then acidified with the same carboxylic acid R^4-CO_2H designated for the target α-aminoacid diamides **5**, which heretofore were synthesized in low yield by the classical Ugi reaction of ketones and ammonia.[9] The overall synthesis of diamides **5** can be achieved in moderate-to-good yield in a single-flask operation.[10]

We have further shown that a one-pot, five-component synthesis of Ugi-type diamides could be implemented wherein nitriles, organometallics and primary amines replaced the amine and carbonyl components of traditional Ugi condensations. By reacting metallated ketimine **3** with a CH_3OH solution of R^4CO_2H (4.5–5.5 equiv) and R^3NH_2 (2.0 equiv), the amine–imine interchange reaction of N-unsubstituted ketimine **4** could be exploited, which was expected to favor the N-substituted imine **6** (Scheme 3). The addition of R^5NC then transformed **6** to the corresponding N-substituted α-aminoacid diamides **7**.



Scheme 3.

Table 2 presents several examples of the 5CC process using representative commercially available substrates to demonstrate its scope. Most reactions afforded a ca 85:15 mixture of the desired 5CC product **7** along with the corresponding 4CC product **5**. Control experiments established that this ratio corresponded to the equilibrium mixture of imines **6** and **4**. Attempts to sequester the ammonia using molecular sieves or zeolites failed to improve this ratio. However, the desired 5CC products **7** were readily obtained pure by flash column chromatography.[11]

In the 5CC reaction leading to **7e**, the major product was the corresponding 4CC N-unsubstituted diamide of general structure **5** (50%). The low yield of 5CC product could be due to slow amine–imine interchange, or to the reduced reactivity of the α-branched *N*-cyclohexyl imine of general formula **6**. In fact, a control experiment established that the normal Ugi condensation of 2-heptanone, cyclohexylamine, $PhCO_2H$ and *t*-BuNC in CH_3OH afforded **7e** in 5–10% yield, which strongly suggested that Ugi condensations of ketones and α-branched amines are unfavorable.

In conclusion, this work has demonstrated that it is possible to extend the range of useful starting materials for the Ugi reaction to families of nitriles and organolithium reagents or Grignard compounds. Moreover, N-unsubstituted and N-substituted diamides **5** and **7**, respectively, can be obtained in moderate to good yields. The current method leads to products that are formally ketone-derived Ugi adducts, some of which are frequently inaccessible by standard methods. In addition, the higher dimensionality of 5CC condensations starting

Table 2. Five-component condensations of R^1CN, R^2Met, R^3NH_2, R^4CO_2H and R^5NC leading to diamides **7**

R^1 = (1.4 equiv)	R^2Met = (1.5 equiv)	R^3 = (2 equiv)	R^4 = (4.5–5.5 equiv)	R^5 = (1.0 equiv)	Pdt (yield)
Et	*n*-BuLi	$PhCH_2$	CH_3	Cyclohexyl	**7a** (55%)
Et	*n*-BuLi	*n*-Bu	CH_3	Cyclohexyl	**7b** (43%)
Et	*n*-BuLi	*n*-Bu	CH_3	Morpholino ethyl	**7c** (34%)
n-C_5H_{11}	MeLi	Allyl	Ph	*t*-Bu	**7d** (66%)
n-C_5H_{11}	MeLi	Cyclohexyl	Ph	*t*-Bu	**7e** (6%)
n-C_5H_{11}	*n*-BuMgCl	$PhCH_2$	$(CH_3)_2CH$	*n*-Bu	**7f** (57%)
Et	PhMgBr	Allyl	PhCH=CH	Cyclohexyl	**7g** (60%)
Ph	*n*-BuMgCl	Allyl	$(CH_3)_2CH$	Cyclohexyl	**7h** (40%)

from nitriles should make it possible to synthesize larger collections of diverse, drug-like structures.

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Supplementary data

Additional experimental procedures and complete spectroscopic data for 4CC and 5CC reaction products shown in Tables 1 and 2. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.12.011.

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10. Representative 4CC experimental procedure—Preparation of **5a**: A solution of propionitrile (71 μL, 0.99 mmol) in anhydrous ether (0.4 mL) was added by syringe over 1 min to *n*-butyllithium (1.6 M in hexane, 0.66 mL, 1.1 mmol) in ether (0.4 mL) at 0 °C under argon. The reaction mixture was stirred for 30 min at 0 °C, then concentrated in vacuo and recooled to 0 °C. Anhydrous CH_3OH (0.7 mL) and acetic acid (142 μL, 2.5 mmol) were added, followed by cyclohexyl isocyanide (88 μL, 0.71 mmol). The reaction mixture was warmed to rt and stirred for 24 h. The bulk of CH_3OH was removed in vacuo, then the reaction mixture was diluted with CH_2Cl_2 (10 mL) and saturated sodium bicarbonate (6 mL). The aqueous layer was extracted with CH_2Cl_2 (3×4 mL) and the combined organic layers were washed with saturated NaCl (6 mL). The organic layers were dried with $MgSO_4$, filtered and concentrated in vacuo to an oil, which was purified via silica gel flash column chromatography.
11. Representative 5CC experimental procedure—Preparation of **7a**: A solution of propionitrile (53 μL, 0.75 mmol) in anhydrous ether (0.3 mL) was added by syringe over 1 min to *n*-butyllithium (1.6 M hexane solution, 0.50 mL, 0.80 mmol) in anhydrous ether (0.4 mL) at 0 °C, under argon. After stirring the reaction mixture for 30 min at 0 °C, benzylamine (116 μL, 1.1 mmol), anhydrous CH_3OH (0.5 mL), and acetic acid (138 μL, 2.4 mmol) were added. The reaction mixture was warmed to rt over 1 h, then cyclohexyl isocyanide (67 μL, 0.54 mmol) was added and stirring continued for 24 h. The bulk of CH_3OH was removed in vacuo and the reaction worked up as described for the 4CC process (Ref. 10).