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Palladium and copper catalyzed cyclizations of hydrazine derived Ugi products: facile synthesis of substituted indazolones and hydroxytriazafluorendiones

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ABSTRACT

Indazolones are medicinally relevant targets. Herein we disclose an improved synthesis to *N*′-(acetamido-2-yl)-substituted indazolones with four points of diversity introduced by Ugi-[M]-amination and -amidation. The ring closure can be achieved by either conventional palladium catalysis or with a ligandless copper protocol. When α-unbranched isocyanides were employed the sole cyclization products of the copper catalyzed reactions are the hitherto undescribed 2-hydroxy-3*H*-3,4a,9a-triaza-fluorene-4,9-diones.

Multicomponent reactions (MCRs) are a powerful tool to provide compound libraries for high-throughput screening and hit finding.[1,2] Especially the Ugi-reaction has generated much interest due to its synthetic potential and its capacity to generate highly diverse products of medicinal relevance, that is, heterocycles and compounds with peptide like moieties. In order to further enhance the diversity a plethora of different methods have been used for postmodification of multi-component reaction products.[3]

Indazolone derivatives have attracted increasing attention due to their promising pharmacological properties,[4,5] including anti-inflammatory,[6] antiallergic,[7] antipsychotic,[8] hypolipidemic[9] and cytostatic[10] activities. A variety of synthetic routes have been reported,[4,11] but all of these require multiple steps and in some cases the use of dangerous intermediates. The only multicomponent reaction based synthesis following the UDC (Ugi-deprotection-cyclization) strategy has been published by Tempest et al. (Scheme 1).[12] It consists of an Ugi reaction (U-4CR) with Boc-protected hydrazine as amine component and 2-fluoro-5-nitrobenzoic acid as acid component, followed by Boc removal of the Ugi product and subsequent nucleophilic aromatic substitution (U-4CR-S_NAr, Scheme 1). The major drawback of this sequence is the need for the strong acceptor in the cyclization step to work which restricts the diversity of the product space accessible with readily available starting materials considerably. Furthermore the nitro group is among those functionalities medicinal chemistry to avoid.[13]

Herein we want to report an improved protocol obviating the aforementioned problems. It comprises an Ugi reaction of a protected hydrazine (**2**, R^2 = Boc or Bn) and an *o*-bromo- or *o*-iodobenzoic acid (**1**), an oxo compound (**3**, ketone or aldehyde) and an isocyanide (**4**, R^5) followed by a transition metal catalyzed cyclization (Scheme 2). Such cyclizations, especially palladium-mediated ones, have been successfully employed for MCR postmodifications on numerous occasions.[14]

In a preliminary experiment equimolar amounts of Boc-protected hydrazine, isobutyraldehyde, *o*-bromobenzoic acid and *tert*-butyl isocyanide were stirred in methanol (1 M) at room temperature. The reaction went smoothly and the Ugi product **5a** was isolated with 94% yield (Scheme 3, entry 1). Subsequent deprotection with 20% trifluoroacetic acid in dichloromethane yielded the free hydrazide **6a** which was subjected to varied cyclization conditions selected from procedures reported in literature.[15–17] Entries 1–3 in Table 1 show results of a starting catalyst (ligand) variation. Only the $Pd_2dba_3/P(^tBu)_3$ system gave complete conversion and

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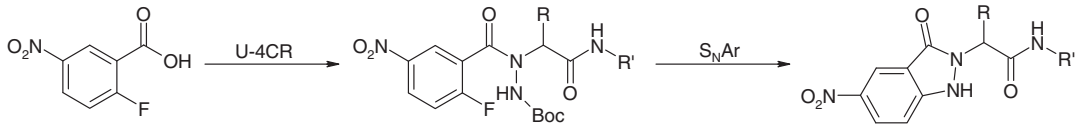
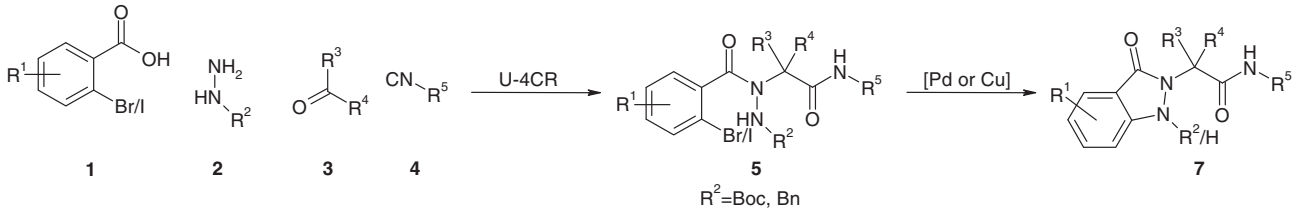
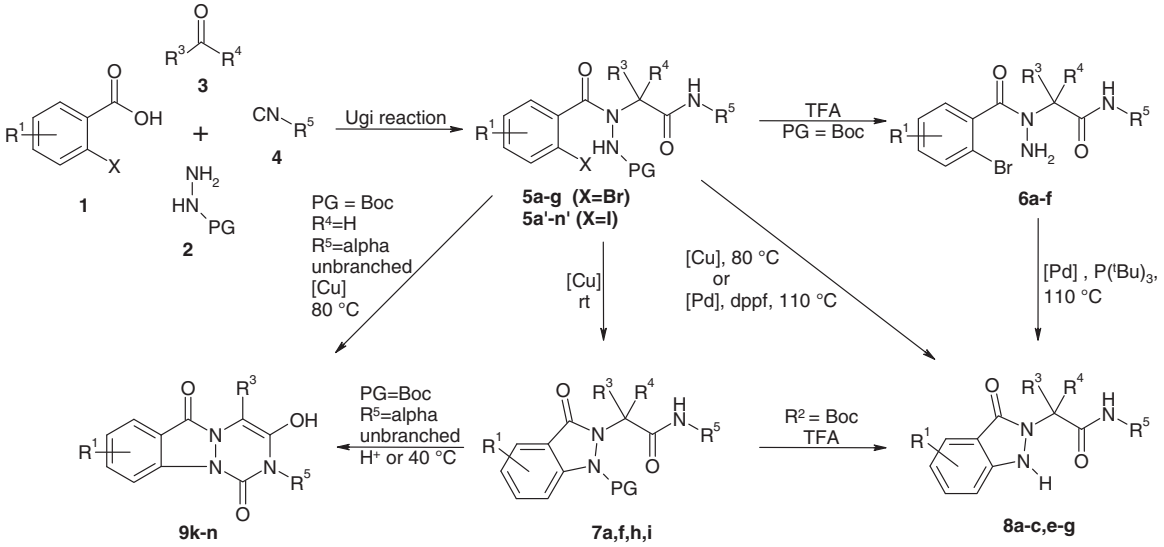


Scheme 1. Indazolone synthesis via Ugi-S$_N$Ar-strategy[12] (R = substituents derived from aldehyde (R) or isocyanide (R′) starting materials).



Scheme 2. Indazolone synthesis via Ugi reaction and palladium or copper catalysed amidation/amination.



Scheme 3. General reaction scheme.

Table 1
Screening of catalysts and conditions for the Pd-catalyzed cyclization of **5a**/**6a** to indazolone **8a**

Entry	Catalyst	Base	s.m.	HPLC yield[a]
1	5 mol % $Pd(PPh_3)_4$	1.4 equiv Na^{t}OBu, 1.6 equiv K_2CO_3	**6a**	59%
2	3.5 mol % $Pd(OAc)_2$, 5 mol % dppf	1.4 equiv Na^{t}OBu	**6a**	40%
3	10 mol % Pd_2dba_3, 5 mol % P(^{t}Bu)$_3$	2 equiv Na^{t}OBu 2 equiv K_2CO_3	**6a**	82%[b]
4	5 mol % Pd_2dba_3, 6 mol % BINAP	2 equiv NaOPh 2 equiv Cs_2CO_3	**5a**	64%
5	2 mol % Pd_2dba_3, 10% xantphos	2 equiv Cs_2CO_3	**5a**	>99%
6	2 mol % Pd_2dba_3, 10 mol % dppf	2 equiv Na^{t}OBu	**5a**	>99%

All reactions were performed in anhydrous toluene under nitrogen at 110 °C.
[a] 254 nm.
[b] Isolated yield after chromatography: 71% (see Table 2).

yielded the desired indazolone **8a** without side products (isolated yield 71%).

This catalytic system (entry 3) was used to synthesize compounds **7g** and **8a–f** (vi), but it turned out that other conditions would allow the direct, one step conversion of the Ugi products to the desired cyclization products **8** without a dedicated deprotection step. If alternatively cyclization conditions could be found that leave the protecting group in place, this would retain the possibility to further elaborate the products without having to re-protect the nitrogen again. Therefore N′-protected **5a** was directly subjected to the above cyclization conditions (cf. Table 1, entry 3) but gave only traces of **8a** with the majority of the starting material unchanged. In a control experiment without palladium we observed a slow deprotection of **5a** producing **6a** indicating that only after thermal cleavage of the Boc group a cyclization of the free amine occurs. As the current catalytic system was obviously unsuitable for our purpose, different ligands and conditions were tested[17] (Table 1, entries 4–6). Both xantphos/Cs_2CO_3 (entry 5)

Table 2
[Pd]-cyclizations: X = Br, 10 mol % Pd_2dba_3, 5 mol % P^tBu_3, 2 equiv NaO^tBu, 2 equiv Cs_2CO_3, dry toluene, 110 °C, overnight

Entry	R	PG	R^3, R^4	R^5	Ugi-4CR		DeBoc-Ugi		Product (isolated yield)	
1	H	Boc	^{i}Pr, H	^{t}Bu	**5a**	94%	**6a**	51%	**8a**	71%
2	H	Boc	^{i}Pr, H	4-Cl-Ph	**5b**	64%	**6b**	61%	**8b**	20%
3	H	Boc	^{i}Pr, H	4-MeO-Bn	**5c**	86%	**6c**	34%	**8c**	16%
4	H	Boc	–$(CH_2)_5$–	^{t}Bu	**5d**	36%	**6d**	Degr.	—	
5	5-NO_2-	Boc	^{i}Pr, H	^{t}Bu	**5e**	70%	**6e**	83%	**8e**	52%
6	5-MeO-	Boc	^{i}Pr, H	^{t}Bu	**5f**	79%	**6f**	69%	**8f**	25%
7	H	Bn	^{i}Pr, H	^{t}Bu	**5g**	11%	n.a.		**7g**	77%

Table 3
[Cu]-cyclizations: X = I, PG = Boc; 5 mol % CuI, 2 equiv Cs_2CO_3, dry DMF

Entry	R^1	R^3, R^4	R^5	Ugi-4CR		Cyclization conditions	Product (isolated yield)	
1	H	^{i}Pr, H	^{t}Bu	**5a′**	73%	A	**7a**	93%
2	H	^{i}Pr, H	^{t}Bu	**5a′**	73%	B	**7a**	95%[a]
3	5-MeO	^{i}Pr, H	^{t}Bu	**5f′**	95%	A	**7f**	12%
4	H	Me,Me	^{t}Bu	**5h′**	73%	A	**7h**	77%
5	H	^{i}Pr, H	Ph	**5i′**	90%	A	**7i**	67%
6	H	^{i}Pr, H	CH_2CH_2OMe	**5k′**	82%	A	**7k′**	Degr.
7	H	^{i}Pr, H	Bn	**5l′**	91%	A	**9l**	57%
8	H	^{i}Pr, H	^{t}Bu	**5a′**	73%	C	**8a**	55%
9	H	^{i}Pr, H	^{t}Bu	**5a′**	73%	D	**8a**	59%
10	5-NO_2	^{i}Pr, H	^{t}Bu	**5e′**	77%	C	**8e**	99%
11	5-MeO	^{i}Pr, H	^{t}Bu	**5f′**	95%	C	**8f**	38%
12	H	^{i}Pr, H	Ph	**5i′**	90%	C	**8j**	Degr.
13	H	^{i}Pr, H	CH_2CH_2OMe	**5k′**	82%	C	**9k**	75%
14	H	^{i}Pr, H	Bn	**5l′**	91%	C	**9l**	55%
15	H	^{i}Pr, H	4-MeO-Bn	**5m′**	77%	C	**9m**	82%
16	H	^{i}Pr, H	4-F_3C-Bn	**5n′**	48%	C	**9n**	61%

Conditions: **A**: rt; **B**: rt, 10 mol % 1,10-phenanthrolin; **C**: 80 °C; **D**: 80 °C, 10 mol % 1,10-phenanthrolin.
[a] HPLC yield (254 nm).

and dppf/NaO^tBu (entry 6) led to a clean and complete conversion of **5a** to **8a** with intrinsic deprotection but the latter one was considerably faster (36 and 14 h, respectively).

With this catalytic system (Table 1, entry 3) we examined the scope and versatility of this sequence (Table 2). The Ugi products were obtained in moderate to good yields. The cyclization works for both electron deficient and electron rich benzoic acids but the yield of the latter suffers from increased side product formation (Table 2, entries 1, 5, 6). Besides aliphatic aldehydes ketones can be easily employed in the Ugi reaction but the deprotected bisamide **6d** degraded during final purification on silica (Table 2, entry 4, cf. Table 3, entry 4). The use of different isocyanides was somewhat hindered by incomplete conversions during the cyclization (Table 2, entry 2, 3). *N*′-Alkyl substituted hydrazides are also suitable substrates, but the liberation of the free base from the benzylhydrazine dihydrochloride salt proved to be difficult. Among the bases tested (triethylamine, sodium hydroxide, potassium carbonate) only sodium hydroxide used in situ gave some amounts of **5g** (entry 7). Liberation prior the Ugi reaction failed as well as the use of potassium carbonate and triethylamine in situ.

Finally we were interested if palladium could be substituted by the cheaper copper which is also a well-known catalyst of amide arylations.[18,19] Stirring **5a**′ (the apostrophe denotes the use of aryliodides instead of bromides) in anhydrous DMF under a nitrogen atmosphere with 5 mol % copper iodide, 10 mol % 1,10-phenanthroline and 2 equiv of cesium carbonate[20] for half an hour resulted in a complete and clean conversion of the starting material. Surprisingly no ligand seems to be required for this cyclization: a control reaction without 1,10-phenanthroline performed similar and gave 93% of the still Boc-protected product **7a** along with 4% deprotected **8a** within half an hour. The reaction tolerates both aldehydes and ketones but Ugi products of the latter have a tendency to degrade (hydrolyze?) on silica and therefore have to be purified with care, for example, on basic aluminum oxide. Treatment of **7a** and **7h** with 20% TFA in dichloromethane gave the free indazolone in 46% and 62% yield, respectively.

Phenylic isocyanides worked fine (Table 3, entry 5) but alkyl isocyanides lead to different results: reaction monitoring via HPLC/MS showed a clear conversion also for benzyl isocyanides and 2-methoxyethyl isocyanide to the desired Boc-protected indazolones but these proved to be instable at elevated temperatures. While **7k** degraded already upon heating to 40 °C to several different products (including deprotected indazolone and hydroxytriazafluorendione, vide infra), **7l** was converted to a new product which we identified by HPLC/MS and NMR as hydroxytriazafluorendione **9l**. The same reaction took place when we tried to cleave the Boc-group in situ with 20% TFA.

Intrigued by this unusual behavior of the Boc-group we started to investigate cyclizations at higher temperature. Subjecting **1a**′ to previous cyclization conditions at 80 °C led directly to the free indazolone **8a** irrespective of the presence of 1,10-phenanthroline (Table 3, entries 8 and 9). Reaction monitoring showed that thermal Boc cleavage occurs at a much lower rate than cyclization and that the rate of the latter is strongly dependent on the substituents at the benzoic acid residue: while the reaction of the nitro substituted substrate is finished within a few minutes even at rt, reactions of electron rich aryliodide moieties require several hours at elevated temperatures to achieve complete conversions (entries 10 and 11). In the same order increasing amounts of different, inseparable dimers of the free indazolone were formed which were in the case of **8f** the main product.

When more nucleophilic and sterically less hindered (unsubstituted α-carbon) isocyanides were employed, the aforementioned hydroxytriazafluorendiones were formed in a clean reaction and isolated as the sole products (entries 13–15). Apparently Boc-group acts as intramolecular acylation source annealing a third

cycle by an attack of the secondary amide nitrogen originating from the isocyanide building block initially.

In summary we have developed an improved two-step synthesis for indazolones with an additional point of diversity (a total of four), increased yield and broadened substrate range. It is based on an Ugi reaction and subsequent palladium or copper catalyzed intramolecular coupling. The cyclizing coupling can be applied to both Boc protected, alkyl substituted and free hydrazides. In case of 1-Boc-protectedindazolones with 2-carboxamidomethyl substituent (**5k′–n′**), a spontaneous second cyclization to triazoles gives the hitherto undescribed 2-hydroxy-3*H*-3,4a,9a-triaza-fluorene-4,9-diones as sole products.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.095.

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*Typical procedure for the synthesis of **5a′***:
To 292 mg (4 mmol) of isobutyraldehyde in 4 ml of MeOH, 530 mg (4 mmol)of *tert*-butylcarbazatare added and the mixture is stirred at rt for 2 h. Then 1011 mg (4 mmol)of *o*-iodobenzoic acid and 339 mg (4 mmol)of *tert*-butylisocyanidare added and the reaction mixture is stirred overnight at rt. After evaporation of the solvent the crude product is purified by column chromatography on silica gel (chloroform/methanol = 99.5/0.5→90/10, R_f = 0.20 [chloroform/methanol = 99.5/0.5]) to yield 1.52 g of the title compound (white solid, 73%).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.34–7.29 (m, 1H), 7.02 (t, *J* = 7.4 Hz, 1H), 6.47 (s, 1H), 4.75 (d, *J* = 10.3 Hz, 1H), 2.16–2.03 (m, 1H), 1.32 (s, 9H), 1.24–1.14 (m, 12H), 1.02 (d, *J* = 6.6 Hz, 3H).

*Typical procedure for the synthesis of **7a***:
In a dry Schlenk tube filled with nitrogen, 41.9 mg (77.3 μmol, 1 equiv)of **5a′** are dissolved in 0.5 ml of abs. DMF together with 1.4 mg (7.7 μmol, 10 mol %)of CuI and 28.3 mg (85.0 μmol, 1.1 equiv)of Cs_2CO_3 and stirred at rt until reaction is completed (HPLC). Then the reaction mixture is filtered through celite, stripped of its solvent and purified by column chromatography on silica (ethyl acetate/hexane = 1/4, R_f = 0.45) to yield 28.1 mg of the title compound (white solid, 93 %).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.87 (dd, *J* = 8.1, 3.0 Hz, 2H), 7.68–7.62 (m, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 4.00 (d, *J* = 11.3 Hz, 1H), 2.96–2.83 (m, 1H), 1.64 (s, 9H), 1.38 (s, 9H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.64 (d, *J* = 6.5 Hz, 3H).

*Typical procedure for the synthesis of **8a***:
In a dry pressure tube filled with nitrogen 158 mg (0.43 mmol, 1 equiv) of **6a** are dissolved in 5 ml of abs. Toluene together with 39.9 mg (43 μmol, 10 mol %) of Pd_2dba_3, 4.6 mg (21 μmol, 5 mol %) of P^{t}Bu, 84.3 mg (0.85 mmol, 2 equiv) of NaO^{t}Bu and 118 mg (0.85 mmol, 2 equiv) of K_2CO_3 and stirred for 18 h at 110 °C. Then the reaction mixture is filtered through celite, stripped of its solvent and purified by column chromatography on silica (ethyl acetate/hexane = 1/1→9/1, R_f = 0.26 [ethyl acetate/hexane = 1/1]) to yield 87.3 mg of a brown solid (71%).^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.23 (d, *J* = 8.2 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 5.11 (d, 2 rotamers: *J* = 9.8, 4.2 Hz, 1H), 2.61–2.47 (m, 1H), 1.38 (s, 9H), 1.10 (d, *J* = 6.7 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H).

*Typical procedure for the synthesis of **9m***:
In a dry Schlenk tube filled with nitrogen 202 mg (0.34 mmol, 1 equiv) of **5m′** are dissolved in 3 ml abs. DMF together with 3.7 mg (0.017 mmol, 5 mol %) of CuI and 128 mg (0.38 mmol, 1.1 equiv) of Cs_2CO_3 and stirred for 15 h at 80 °C. Then the reaction mixture is filtered through celite, stripped of its solvent and purified by column chromatography on silica (ethyl acetate/hexane = 1/2, R_f = 0.25) to yield 107 mg (82 %).^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (d, *J* = 7.3 Hz, 1H), 7.71–7.62 (m, 2H), 7.37–7.31 (m, 1H), 7.23 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.62 (d, *J* = 15.0 Hz, 1H), 4.57 (d, *J* = 15.0 Hz, 1H), 3.69 (s, 3H), 2.18–2.06 (m, 1H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.62 (d, *J* = 6.9 Hz, 3H).