

Raising the diversity of Ugi reactions through selective alkylations and allylations of Ugi adducts

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10 **Keywords:** Ugi reaction; allylation; palladium; Tsuji-Trost reaction; metathesis; piperidines.

11 **Abstract:** We report here selective Tsuji-Trost type allylation of Ugi adducts using a strategy
12 based on the enhanced nucleophilicity of amide dianions. Ugi adducts derived from aromatic
13 aldehydes were easily allylated at their peptidyl position with allyl acetate in the presence of
14 palladium catalysts. These substitutions were compared to more classical transition metal free
15 allylations using allyl bromides.

16

17 1 Introduction

18 Since its discovery and even more after the 1980's, the Ugi reaction has fascinated chemists with the
19 high diversity brought by its four components nature together with its impressive functional tolerance
20 (Dömling and Ugi, 2000; Hulme and Gore, 2003; Orru and de Greef, 2003; Zhu and Bienaymé,
21 2005; Dömling, 2006; Dömling et al., 2012; Zhu et al., 2014; Boyarskiy et al., 2015; Váradı et al.,
22 2016; Lei et al., 2018). Besides important efforts devoted to the preparation of libraries of
23 heterocycles through cyclization of properly functionalized Ugi adducts (Tempest, 2005; Sunderhaus
24 and Martin, 2009; Ivachtchenko et al., 2010; Orru and Ruijter, 2010; 2010; Sadjadi and Heravi, 2011;
25 Eckert, 2012; Sharma et al., 2015), a number of studies have focused on raising the diversity by
26 letting Ugi adducts react in further intermolecular couplings (Elders et al., 2009; Brauch et al., 2010;
27 Zarganes-Tzitzikas et al., 2015; Zarganes-Tzitzikas et al., 2015; Kaur et al., 2016). In contrast with
28 the previous intramolecular couplings, these strategies (such as the combination of MCRs) are much
29 more sensitive to steric hindrance and require more attention in selecting the functionalities required
30 for further couplings. For this reason, most transformations involving the peptidyl position of Ugi
31 adducts are limited to intramolecular reactions (Bossio et al., 1997; Trifilenkov et al., 2007; Salcedo
32 et al., 2008; El Kaïm et al., 2011; Tyagi et al., 2013; Zhang et al., 2013; Ben Abdessalem et al., 2015;
33 Ghandi et al., 2015; Vachhani et al., 2015; Li et al., 2016). We recently proposed a dianionic amide
34 strategy to raise the nucleophilic behaviour of Ugi adducts derived from aromatic aldehydes and
35 demonstrated the interest of this approach using bis-electrophilic derivatives prone to trap the

36 dianions and form heterocycles (scheme 1) (Zidan et al., 2017; Zidan et al., 2018). Following the
37 high yielding cyclizations observed in these studies, we decided to explore more thoroughly the
38 synthetic potential of these dianions (Thompson, 1994; Langer and Freiberg, 2004) towards more
39 simple electrophiles. We now wish to report further applications of this chemistry in Tsuji-Trost
40 reactions as well as metal-free alkylations with bromide derivatives (Scheme 1).

41 Scheme 1

42 2 Results and discussion

43 Following our interest in Tsuji-Trost reactions involving isocyanide based MCRs (Dos Santos and El
44 Kaïm, 2014; Cordier et al., 2015; El Mamouni et al., 2016), we decided to explore the behaviour of
45 Ugi adducts dianions towards allyl acetate. Besides the efficiency and regioselectivity issues of the
46 reaction of these dianions with π -allyl palladium complexes, such study might bring interesting
47 pathways for further enantioselective approaches. For this study, Ugi adduct **1a** was selected due to
48 its good behaviour in our previous studies with propargyl bromide and diiodomethane. It was
49 prepared in 89% yield from 4-chloro-benzaldehyde, propylamine, acetic acid and *tert*-
50 butylisocyanide. (Table 1). When **1a** was heated with allyl acetate in THF using 2.5 equivalents of
51 potassium *tert*-butoxide together with a Pd(dba)₂/PPh₃ catalytical couple, we were delighted to
52 observe a selective C-allylation of **1a** giving **3a** in 65% isolated yield after 2 hours refluxing (entry 1,
53 Table 1).

54 Table 1.

55 Different bases in various solvents were then evaluated using the same palladium/phosphine couple.
56 The enhanced nucleophilicity of the 1,3-amide dianion towards the π -allyl palladium cationic
57 complex was confirmed experimentally by comparing the use of 2.5 and 1.3 equiv of KHMDS
58 (affording respectively 93% and 37% isolated yields : entries 4 and 5, Table 1). NaH in DMSO, gave
59 the best conditions affording to our delight a nearly quantitative yield of **3a** in only one hour at room
60 temperature (entry 9, Table 1). Further modifications of the catalyst using more complex phosphines
61 led to longer reaction time and lower yields (entries 10-12, Table 1), while in absence of palladium
62 source, no product was observed (entry 13, Table 1).

63 A set of Ugi adducts were then prepared in methanol and submitted to these optimized allylation
64 conditions. The results are gathered in Scheme 2. As observed in our previous studies (Zidan et al.,
65 2017; Zidan et al., 2018), an aryl group tethering the peptidyl position is required for efficient
66 allylation. Indeed, Ugi adduct **1j** prepared from isovaleraldehyde failed to form the expected **3j**
67 probably due to the inability to form the dianionic intermediate with this less acidic substrate.
68 Surprisingly, we didn't observe much correlation between yields and the electronic nature of the
69 aldehyde as shown by the similar yields obtained with both 4-nitro or 4-methoxy substituted
70 derivatives **3b** and **3c**. A much stronger effect of the substitution partner of the aromatic moiety was
71 observed with 2-chloro substituted Ugi adduct **1h** which failed to give any adduct under these
72 conditions as observed with **1j**. The same behaviour was observed for the attempted synthesis of the
73 fluoro analogue **3i**. This lack of reactivity can probably be explained by the steric hindrance brought
74 by substituents at the ortho position preventing to reach the planar geometry required for benzylic
75 anion stabilization. Initial trials on enantioselective allylations were rather deceiving. When
76 triphenylphosphine was replaced by BINAP (5mol %) for the reaction of **1a** with **2a**, **3a** could be
77 formed rapidly in good yield (89%) but poor enantioselectivity (5%) whereas the use of Trost ligand
78 (DACH-phenyl) failed to give any allylation reaction. A wider scope of chiral ligands as well as

79 alternative solvents allowing lower temperatures will have to be evaluated to reach an
80 enantioselective version. The reaction could not be extended to more substituted allylic acetate
81 derivatives such as cinnamyl acetate. The latter failed to react with Ugi adduct **1a** even under
82 prolonged heating, leading only to saponification of the ester and isolation of cinnamyl alcohol.

83 Scheme 2.

84 Submitting propargylamine-derived Ugi adduct **1s** to the same reaction conditions didn't afford any
85 allylated product but resulted in the clean formation of 2,3-dihydropyrrole **4** (Scheme 3), a reaction
86 already reported by Miranda *et al.* in 2012 (Polindara-García and Miranda, 2012). They could isolate
87 the same dihydropyrrole **4** in 36% yield treating **1s** with *t*-BuOK (2.5 equiv) in THF, while we could
88 obtain 79% yield with our conditions. This selectivity was not very surprising when considering the
89 respective intra and intermolecular properties of the two pathways. However, the ability to form
90 enyne derivatives from Ugi adducts together with the interest of reversing a preferred selectivity were
91 challenging enough to explore different set of conditions. Indeed, the dihydropyrrole formation
92 probably involves a first isomerization into allene followed by further 5-endo-trig cyclization. This
93 could leave some space for a previous intermolecular allylation if the lifetime of the dianion could be
94 reduced by increasing the kinetic of the allylation step. Introducing the allyl acetate together with the
95 palladium catalyst and the Ugi adduct in DMSO followed by the addition of the base resulted in a
96 lower 54% yield of **4** together with a complex mixture of allylated products. We next explored the
97 use of allyl bromide as a potential electrophilic species in the absence of palladium. When adding the
98 latter to Ugi adduct **1s** followed by NaH, we were delighted to observe the expected enyne **3s**
99 obtained in 58% isolated yield without any trace of dihydropyrrole (Scheme 3). This interesting
100 control of the selectivity offers an attractive access to enyne derivatives for further cyclization
101 studies.

102 Scheme 3.

103 These conditions settled with allyl bromide proved useful as well for the reaction of other alkyl
104 bromides and iodides as shown in Scheme 4. The lowest 30% yield of **6c** obtained using 3-
105 bromocyclohex-1-ene may be explained by the use of secondary halides together with the high steric
106 hindrance around the peptidyl position of the Ugi adduct. In order to confirm further the importance
107 of forming dianionic intermediates, the formation of **3a** was attempted using allyl bromide in excess
108 (1.5 equiv) but reducing the amount of sodium hydride to 0.9 equiv. In this case, only traces of
109 allylated compound could be identified after 2h at rt whereas the reaction was completed after the
110 same time when using 2.5 equiv of sodium hydride. Interestingly, whereas under Tsuji-Trost type
111 conditions we couldn't observe any allylation of both 2-chloro and 2-fluoro substituted derivatives **1h**
112 and **1i**, the latter gave us a moderate 40% isolated yields of **3i** when using just sodium hydride with
113 allyl bromide.

114 Scheme 4.

115 A further interest of the use of palladium free conditions may be found in the ability to carry the
116 reaction starting directly from the four Ugi components. Indeed remaining isocyanides after the Ugi
117 reaction are potentially inhibitor for most classical palladium catalyzed processes making thus one-
118 pot processes difficult to achieve (El Kaim *et al.*, 2008).¹ After completion of the Ugi adduct, the

¹ However, one-pot processes may be envisioned if the remaining isocyanide is destroyed by an acidic hydrolysis prior palladium addition.

119 methanol was evaporated under reduced pressure. The solvent was then replaced by DMSO. Addition
120 of sodium hydride followed by allyl bromide afforded the final allylated Ugi adducts in good overall
121 yields (Scheme 5).

122 Scheme 5.

123 With this easy allylation of Ugi adducts in hand, we decided to take advantage of the diversity
124 offered by the latter coupling to explore Ugi/allylation/Ring Closure Methathesis (RCM) strategies
125 towards various nitrogen based heterocycles. The use of RCM as Ugi post-condensation has already
126 demonstrated its power for the formation of 5, 6-membered heterocycles as well as macrocyclic
127 derivatives (Banfi et al., 2003; Beck et al., 2003; Hebach and Kazmaier, 2003; Ribelin et al., 2007;
128 Ku et al., 2011). However the synthetic potential of these strategies is in a way limited by the need of
129 introducing the two allylated moieties at an early stage which reduces the diversity offered by the
130 two-step process. The late stage allylation we propose is highly versatile allowing to settle the
131 strategy with a single alkenyl moiety in the starting components. Thus using allyl amine, we could
132 easily prepare a library of piperidines with five points of diversity (Scheme 6).

133 Scheme 6.

134 This access to 3,4-dehydropiperidine derivatives **7** could be further enriched by a potential
135 isomerisation into cyclic enamines as demonstrated by the ruthenium hydride catalysed conversion of
136 **7a** into **8** (Scheme 6). The versatility of the method can be pictured by the alternative choice of the
137 alkenyl moiety on the acidic component such as in cinnamic acid offering now a very simple access
138 to 3,4-dehydropiperidine-2-one **9** (Scheme 7).

139 Scheme 7.

140 **3 Conclusion**

141 In summary, we have extended the potential of the Ugi reaction using 1,3-amide dianionic species as
142 intermediates for efficient allylations at the peptidyl moiety of Ugi adducts. The procedure raises the
143 diversity of Ugi adducts and offers unique opportunities for the preparation of nitrogen based
144 heterocycles through association with ring closure metathesis. The power of the latter strategy has
145 been demonstrated by the preparation of various piperidines which are important scaffolds for
146 medicinal applications.

147

148

149 **Scheme 1.** Reaction of Ugi amide dianion with mono and biselectrophiles.

150 **Scheme 2.** Scope of the Ugi/Tsuji-Trost cascade

151 **Scheme 3.** Allylation of Ugi propargyl adduct.

152 **Scheme 4.** Scope of alkylating agents

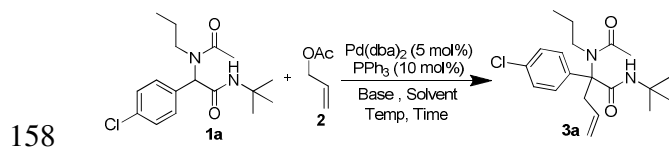
153 **Scheme 5.** Cascade one pot reaction

154 **Scheme 6.** Ugi/allylation/RCM strategy

155 **Scheme 7.** Ugi/allylation/MCR towards piperidones

156 **3.1 Tables**

157 **Table 1. Screening of various conditions^a**



Entry	Base (equiv)	Solvent	Temp (°C)	Time (h)	Yield (%)
1	<i>t</i> -BuOK(2.5)	THF	reflux	2	65
2	<i>t</i> -BuOK(2.5)	DMF	70	12	70
3	KHMDS (2.5)	THF	reflux	1	95
4	KHMDS (2.5)	THF	50	1	93
5	KHMDS (1.3)	THF	50	1	37
6	KHMDS (2.5)	THF	rt	1	88
7	NaH (2.5)	THF	reflux	12	45
8	NaH (2.5)	DMF	70	12	50
9	NaH (2.5)	DMSO	rt	1	96
10 ^b	NaH (2.5)	DMSO	rt	12	Traces
11 ^c	NaH (2.5)	DMSO	rt	12	80
12 ^d	NaH (2.5)	DMSO	rt	1	94
13 ^e	KHMDS (2.5)	THF	rt	12	-

159 ^aReaction conditions: **1a** (0.5 mmol), **2** (0.75 mmol), Pd(dba)₂ (0.025 mmol) and PPh₃ (0.05 mmol)
 160 in solvent (0.5 M).^bUsing Xantphos (5 mol%) instead of PPh₃. ^cUsing Johnphos (10 mol%) instead of
 161 PPh₃. ^dUsing Pd(PPh₃)₄ (5 mol%) instead of Pd(dba)₂/PPh₃. ^eReaction without Pd(dba)₂ and PPh₃.

162

163 **4 Conflict of Interest**

164 *The authors declare that the research was conducted in the absence of any commercial or financial*
165 *relationships that could be construed as a potential conflict of interest.*

166 **5 Author Contributions**

167 AZ was responsible for designing and performing the experiments. AZ, AMLN, NEAAES, AKA and
168 LEK discussed the evolution of the project and revised the manuscript together, LEK and AKA
169 directed the project and wrote the publication.

170 **6 Acknowledgment and dedication**

171 We dedicate this work to our colleague Mohamed Ali Hassan who passed away few months before
172 the end of this study. We gratefully acknowledge a Scholarship from the Egyptian Government,
173 which was awarded to A. Zidan.

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