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Photo-induced coupling of tertiary amines with Ugi-derived dehydroalanines as a practical device in the synthesis to 2,4-diaminobutyric acid derivatives

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ABSTRACT

An Ir-mediated photocatalytic coupling of tertiary amines with Ugi-dehydroalanines was developed as an entry to medicinally important 2,4-diaminobutyric acid derivatives. In the process the 2,4-diaminobutyric acid framework is assembled directly embedded into a peptoide structure, via the construction of the $C_3(sp^3)$–$C_4(sp^3)$ bond, through a C—H functionalization. The photocatalyzed oxidation of the tertiary amine produce a free radical intermediate which reacts with the double bond present in the dehydroalanines. The complete protocol comprises an Ugi 4-CR followed by an elimination reaction and the photo-induced coupling. Using this strategy, 15 new diversely substituted unnatural α,γ-diamino acids peptide derivatives were prepared in low to good yields.

L-2,4-Diaminobutyric acid **1** (L-DABA) [1] is a neurotoxic naturally occurring non-proteinogenic diamino acid found in significant quantity in certain *Lathyrus* and related seeds (Fig. 1) [2]. It is also an important component of particular bacterial cell walls [3]. Although this amino acid is not frequently incorporated into protein chains, it is an important molecular motif found in a number of natural peptide antibiotics, including members of the non-ribosomal cyclic polypeptide polymyxin family [4]. Polymyxins B (**2** and **3**) and E (colistin) which include up to six L-DABA units, are used as the last therapeutic alternative for the treatment of multidrug-resistant *Pseudomonas aeruginosa, Acinetobacter baumannii, and Klebsiella pneumoniae* [5]. Among other important peptide antibiotics incorporating L-DABA units are polypeptin [6] and comirin [7]. L-DABA is commercially available and is generally used in classic stepwise peptide coupling sequences when necessary. Furthermore, synthesis of the 2,4-diaminobutyric acid derivatives involves reaction of an amine source, either by a substitution process with methyl 4-bromo-2-phthalimidobutyrate, or via the ring-opening process of *N*-acylated-2-amino-4-butyrolactones [8]. Michael addition of the enolate of glycine derivatives to nitroalkenes gives access to 2-substituted-4-diaminobutyric acids (after reduction) through the construction of the C_2-C_3 bond [9]. Other syntheses involves the Hofmann degradation [10] or the Curtius [11] and Schmidt reactions of glutamic acid [12]. Interestingly, a formal cycloaddition between simple ethyl acrylate and diazomethane has also been described to generate the DABA ethyl ester, after a reductive ring opening process of the pyrazoline intermediate [13].

On the other hand, due to its balance between stability and reactivity, the double bond in dehydroalanine (Dha) scaffolds **6** is a unique synthetic platform for further modifications. In this context, in the last years post-translationally modified proteins have been accessed by the direct functionalization of dehydrolanine double bonds [14,15]. The olefin present in the Dha has served as a pivotal template for various synthetic transformations such as polar and radical additions, metal-catalyzed cross-couplings, and cycloadditions [16]. The direct radical addition to Dha's holds special significance because this process allows formation of a new C—C bond, and reaction conditions utilized for this purpose range from the use of classic Bu_3SnH as propagator [17] to metal-catalyzed processes [18]. Along this line, Jui and coworkers recently developed a photocatalytic method for the direct addition of tertiary amines (**4**) to Dha derivatives (**6**) via the SET-induced generation of an α-amino radical intermediate **5** through a C—H functionalization (Scheme 1) [19]. It is important to note that this highly valuable process assembles the DABA framework directly embedded into a peptide structure, via the construction of the $C_3(sp^3)$–$C_4(sp^3)$ bond (Scheme 1).

As part of our ongoing program to the diversification of Ugi-derived Dha's **6** [20], we observed that a tertiary amine could undergo also photocatalytic-induced reductive addition to the

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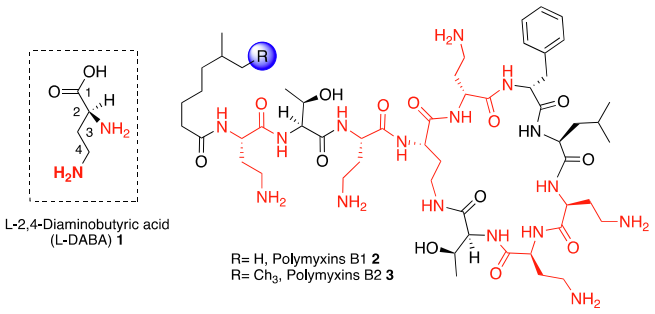
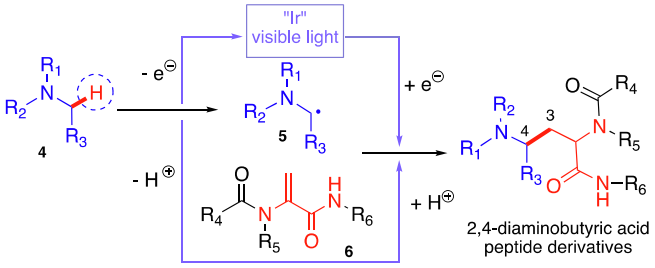


Fig. 1. l-2,4-Diaminobutyric acid (L-DABA) and polymyxins B.



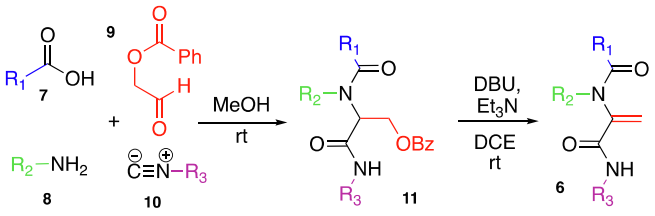
Scheme 1. Photocatalytic addition of tertiary amines to Dha derivatives.

double bond of these readily available substrates (Table 2). Furthermore, considering that earlier we had demonstrated that dehydroalanines **6** could be prepared by using an Ugi four-component reaction (Ugi 4-CR) followed by an elimination process (Table 1) [21], the protocol might represent a practical three-step entry to diversely substituted peptide-DABA libraries. Diversification vectors would result simply by the judicious choice of the starting four component-input set in the Ugi-4CR. Herein, we address this task and describe our earlier results of the development of a photocatalytic-induced addition of tertiary amines to Ugi-derived dehydroalanines.

We started our investigation with the synthesis of different Ugi adducts under the reported optimized conditions using equimolar amounts of the four components in methanol (1 M) at room temperature, for 24 h (Table 1). As reported earlier the use of the benzoyloxyacetaldehyde **9** was necessary as the aldehyde component since this substitution allows the subsequent elimination process. Complementary commercial benzoic, indoleacetic, acetic and furoic acids were used as the acid components **7**. Furthermore, amines such as 2-Br-benzylamine, *n*-hexylamine, benzylamine, *tert*-butylamine, 3,4-dimethoxybenzylamine, and 4-methoxybenzylamine were chosen to expand diversification of the protocol. Two isocyanides (*tert*-butylisocyanide and cyclohexylisocyanide) completed the four-component set of the study. As described in Table 1, the Ugi reaction proceeded in low to moderate yields (20–65%). Then, with the Ugi adducts in hand, the elimination process of the benzoyloxy group was carried out. After a short optimization process, we found that the reaction showed better performance using a combination of Et_3N and DBU as the basic medium [21]. Thus, under these conditions the corresponding dehydroalanines **6a-l**, were obtained in moderate to good yields (20–95%). In general, the adducts derived from cyclohexyl isocyanide showed improved efficiency as compared to their *tert*-butyl analogs, perhaps owing to steric issues (Table 1).

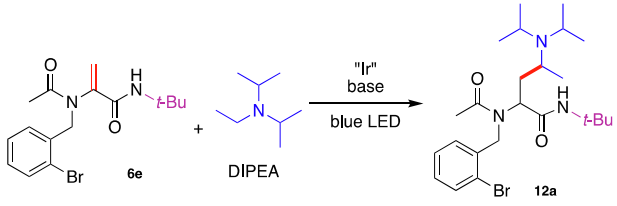
Then, we began the investigation of the optimal reaction conditions for the proposed photocatalytic coupling process to obtain the 1,4-DABA peptoide scaffolds via the $C_3(sp^3)$–$C_4(sp^3)$ bond formation. To this end, dehydroalanine **6e** and *N*′,*N*-diisopropylethylamine (DIPEA, Hünig base) were utilized as model substrates. In the first attempt, reaction of 1.5 equivalents of DIPEA and [Ir(dtbbpy)(ppy)$_2$] PF_6 (1% mol) with **6e** gave the expected coupling product **12a** in 36% yield (Table 2, entry 1). In control experiments, we verified that, the reaction did not work in either the absence of light irradiation or in the absence of the photocatalyst (Table 2, entries 2 and 3). We found that acetonitrile provided a greater yield of the expected product **12a** compared with other solvents such as dimethylacetamide, dichloroethane and toluene (entries 4–6). Photocatalysts such as Ir(ppy)$_3$ and Ru(BPY)$_3$ were evaluated, however the [Ir(dtbbpy)(ppy)$_2$]PF_6 complex was found to be the more efficient for the process (entries 7 and 8) [10]. Then, the

Table 1
Ugi 4-CR and the elimination process.



Exp[a]	R_1	R_2	R_3	Yield (%)	
1	Ph-	2-Br-Bn-	*t-Bu*	**11a** (30)	**6a** (42)
2	Ind-CH_2-	2-Br-Bn-	*CyHex*	**11b** (30)	**6b** (76)
3	Ind-CH_2-	$(CH_2)_5CH_3$-	*CyHex*	**11c** (53)	**6c** (54)
4	CH_3	4-OMe-Bn-	*t-Bu*	**11d** (58)	**6d** (94)
5	CH_3	2-Br-Bn-	*t-Bu*	**11e** (30)	**6e** (95)
6	Furan	$(CH_2)_5CH_3$-	*CyHex*	**11f** (58)	**6f** (27)
7	Furan	$(CH_2)_5CH_3$-	*t-Bu*	**11g** (51)	**6g** (46)
8	Furan	2-Br-Bn-	*t-Bu*	**11h** (25)	**6h** (46)
9	CH_3	Bn	*CyHex*	**11i** (37)	**6i** (70)
10	CH_3	Bn	*t-Bu*	**11j** (39)	**6j** (43)
11	CH_3	*t-Bu*	*CyHex*	**11k** (65)	**6k** (59)
12	CH_3	3,4-OMe-Bn-	*t-Bu*	**11l** (26)	**6l** (22)

Table 2
Optimization of the photocatalytic coupling process.



Exp[a]	Photocatalyst	Base[b]	Solvent[c]	Yield (%)
1	[Ir(dtbbpy)(ppy)$_2$] PF_6	–	MeCN	36
2	[Ir(dtbbpy)(ppy)$_2$] PF_6	–	MeCN	NR
3	–	–	MeCN	NR
4	[Ir(dtbbpy)(ppy)$_2$] PF_6	–	DMA	10
5	[Ir(dtbbpy)(ppy)$_2$] PF_6	–	DCM	20
6	[Ir(dtbbpy)(ppy)$_2$] PF_6	–	Toluene	25
7	Ir(ppy)$_3$	–	MeCN	NR
8	Ru(BPY)$_3$	–	MeCN	NR
9	[Ir(dtbbpy)(ppy)$_2$] PF_6	–	MeCN	47
10	[Ir(dtbbpy)(ppy)$_2$] PF_6	DMAP	MeCN	44
11	[Ir(dtbbpy)(ppy)$_2$] PF_6	DBU	MeCN	12
12	[Ir(dtbbpy)(ppy)$_2$] PF_6	Na_2HPO_4	MeCN	43
13	[Ir(dtbbpy)(ppy)$_2$] PF_6	Na_2CO_3	MeCN	51

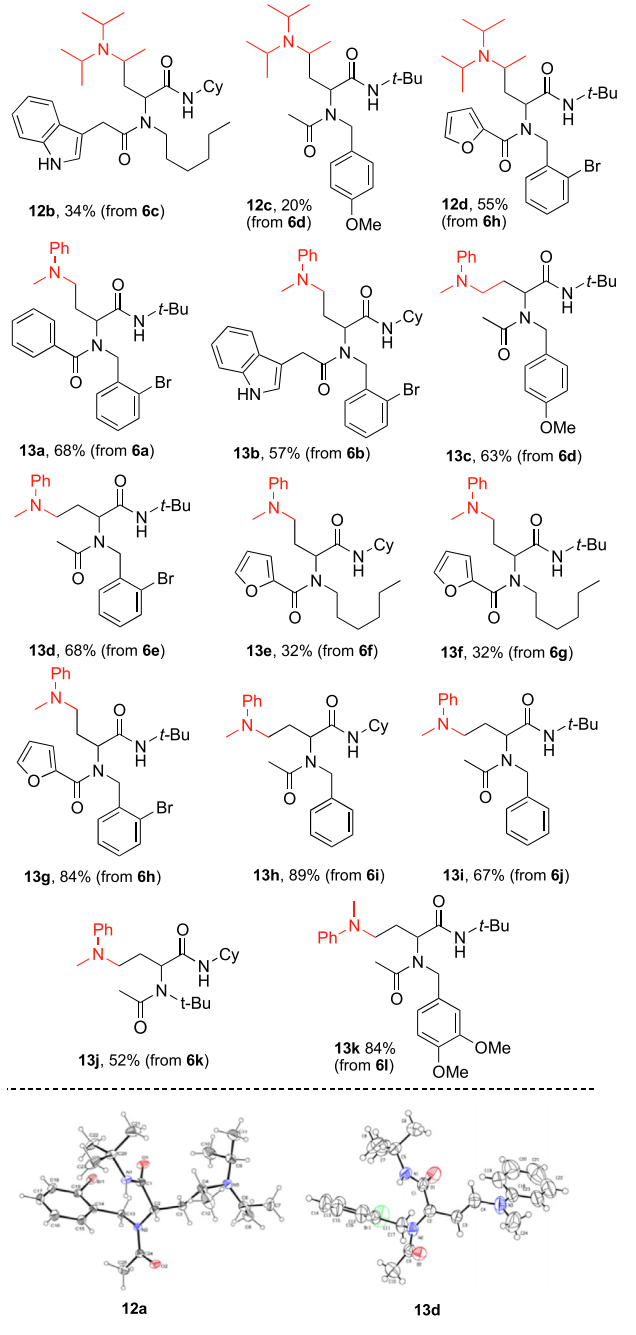
substrate molar ratio was investigated, observing a higher yield when three equivalents of amine and 2 mol% of the iridium photocatalyst were utilized (entry 9). Different organic and inorganic bases such as DMAP, DBU, Na_2HPO_4, Na_2CO_3 were evaluated as additives, with Na_2CO_3 being the most effective with 51% yield of the desired product **12a** (entries 10–13).

At this point, we set up the conditions of entry 13 as the optimal ones and used them in further experiments. It is worth mentioning that at the outset of the study, we faced some problems for the isolation and characterization of compound **12a**, because it was undetectable under UV light. This problem was resolved using ninhydrin stain. The complete identification of the structure of the diastereomer *major*-**12a** was initially carried out by its spectroscopy data and further confirmed by single crystal X-ray analysis [22] (Table 3). The minor diastereoisomer (*minor*-**12a**) was isolated in 13% yield along with 7% of the corresponding dehalogenated product **14** (see Supporting Information).

With the optimized conditions in hand, we set out to synthesize a series of different 2,4-diaminobutyric acid peptide derivatives using the Hünig base. However, as expected this reagent always afforded an inseparable and complicated to identified, diastereoisomeric mixture of the product. For this reason, at this point, we chose to focus on isolating only the major product in further three more examples (**12b-d**, Table 3). Fortunately, diastereoisomeric mixture is not possible when the *N'N*-dimethylaniline is used, and superior yields were observed in the coupling process using this amine. In general good yields (32–89%) were observed in most experiments when the Ugi-derived dehydroalanines were submitted to the photocatalytic coupling conditions. It is important to note that bromo-aromatic derivatives (**12a, d** and **13a, b, d, g**), which might be reactive in related coupling conditions (*e.g.*, Pd-mediated cross-coupling or anionic protocols), proved to be compatible with the photocatalytic conditions. The reaction worked well with dehydroalanines bearing aromatic (with MeO- groups) and heteroaromatic systems such as furan (**12d** and **13e-g**) and indole (**12b** and **13b**) as well as aliphatic chains (**12b** and **13e-f**). However, we did not observe a clear trend regarding how the substituent on the dehydroalanines affected the reaction (Table 3). At this stage, Table 3 demonstrates, at least preliminarily, that the photoredox coupling process provides a straightforward method to incorporate tertiary amines to Ugi-dehydroalanines as an entry to medicinally important 2,4-DABA derivatives. Indeed, the three-step protocol delivered 15 new and interesting derivatives of unnatural α,γ-diamino acid peptoids with diverse substituents.

In summary, an Ir-mediated photocatalytic coupling of tertiary amines with Ugi-dehydroalanines was developed as an entry to medicinally important 2,4-diaminobutyric acid derivatives. This highly valuable process assembles the DABA framework directly embedded into a peptoide structure, via the construction of the $C_3(sp^3)$–$C_4(sp^3)$ bond, through a C—H functionalization. The complete protocol comprises a Ugi 4-CR followed by an elimination reaction and the photo-induced coupling. Using this strategy, 15 interesting new unnatural α,γ-diamino acid peptide derivatives with diverse substitution patterns were prepared. The structure of the 2,4-DABA derivatives might be adjusted by a judicious choice of the starting four component-input set in the Ugi-4CR. This study streamlines the photocatalytic-induced formation of an α-amino carbon radical and its further functionalization. Further optimization of the protocol and extension to more complex substrates is currently under study in our laboratory.

Table 3
Products of the Ir-mediated photo-induced.



Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151152.

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[22] CCDC 1862754 (for 10e) and CCDC 1915170 (for 11e) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.