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Graphical Abstract

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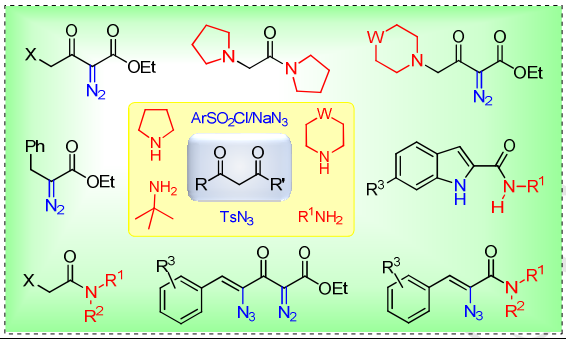

Amine-Mediated Synthesis of Amides from 1,3-Dicarbonyl Compounds through a Domino Diazo Transfer/Aminolysis Process

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Abstract:

The dual role of amines as both catalysts and substrates for the synthesis of diazo compounds or carboxamides from 1,3-dicarbonyl compounds is described herein. In the presence of a suitable diazo transfer agent, primary and cyclic secondary amines act as basic catalysts for the diazo transfer reaction to malonates, β-keto esters, and β-diketones. Depending on the structure of the 1,3-dicarbonyl compound and the nucleophilicity of the amine, the resulting α-diazo-β-keto ester undergoes cleavage of the acyl group to give amides. A multifunctionalized γ-azido-α-diazo-β-keto ester was cleanly prepared in good yields by this one-pot protocol under practical and safe conditions, being employed in a Knoevenagel-type condensation with aromatic aldehydes to give densely functionalized diazo azido compounds. Further treatment of these unsaturated γ-azido-α-diazo-β-keto esters with primary amines readily furnished the corresponding α-azidocinnamamides in high yields, which were used in the synthesis of novel indole-2-carboxamides through the rhodium-catalyzed intramolecular C-H insertion.

Keywords:

Diazo transfer
α-Diazo-β-keto esters
Knoevenagel reaction
α-Azidocinnamamides
Indole-2-carboxamides
Intramolecular C-H insertion

1. Introduction

Contemporary organic synthesis is founded on the design of chemical processes that are not only efficient, selective and reliable, but also environmentally friendly. To be both environmentally and economically acceptable, novel synthetic procedures should eliminate (or drastically reduce) the use and generation of hazardous substances, allowing the set-up and work-up steps to be performed under operationally simple conditions.[1]

Synthetic transformations involving α-diazo carbonyl compounds, including cyclopropanation, cycloaddition, and X-H insertion (X = C, N, O), have received considerable attention due to their versatility, allowing a multitude of carbo- and heterocyclic frameworks of biological and technological importance to be accessed.[2] Reactions involving α-diazo carbonyl compounds include domino processes consisting of sequential arrays of bond-forming and bond-breaking steps, which are frequently performed under mild conditions and are associated with a high thermodynamic driving force generating a single product, together with inoffensive byproducts (N_2 or small stable molecules).[3]

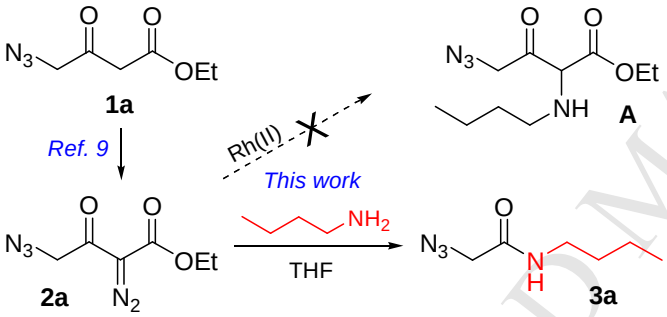
In spite of their recognized versatility as building blocks for the synthesis of carbo- and heterocyclic targets, the wider use of α-diazo carbonyl compounds is, at least in part, hampered by the limited availability of methods that are truly simple, efficient, inexpensive, and safe.[4] The base-catalyzed diazo transfer reactions from sulfonyl azides to 1,3-dicarbonyl compounds remain the most studied method for the preparation of α-diazo carbonyl compounds.[5] Despite its broad applicability, this transformation presents a number of disadvantages, including the use of large amounts of base, toxic solvents, and shock-sensitive chemicals, slow conversions to the product, and the generation of large quantities of residues.[4,6]

In the case of *para*-toluenesulfonyl azide (tosyl azide, TsN_3), this diazo transfer reagent is associated with a risk of explosion during manipulation, due to its sensitivity to mechanical shock.[7] Moreover, the generation of one equivalent of tosyl amide ($TsNH_2$) as the byproduct of the diazo transfer reaction using TsN_3 causes serious issues concerning the isolation and purification of the desired diazo product. While several modified diazo transfer reagents have been designed to avoid the constraints imposed by the use of tosyl azide and its byproduct tosyl amide, most of them are expensive, commercially unavailable or have limited application.[8] Therefore, the development of greener and more effective synthetic methods for the preparation of α-diazo carbonyl compounds is of considerable interest.

During our studies on the preparation and reactivity of functionalized α-diazo carbonyl compounds **2**,[9,10] we were interested in the metal-catalyzed N-H insertion reaction of the metallocarbenoid originating from the diazo **2a** with amines,[11] which would give rise to synthetically useful α-amino-γ-azido-β-keto esters **A** (Scheme 1). Surprisingly, simply mixing

2a and *n*-butylamine in THF for 2 h at r.t. furnished the α-azido acetamide **3a** as the sole product, which was isolated in high yield with no evidence of any product formed by N-H insertion or other transformation. α-Diazo-β-keto esters are known to undergo cleavage of the acyl group in the presence of strong O-nucleophiles (such as the hydroxide ion as well as alkoxides) to give acids and esters.[5b,12] Nonetheless, we envisaged that the use of a nucleophilic amine in this practically unexplored transformation[13] could have synthetic potential as a route to obtaining amides, due to the chemical and biological importance of this class of nitrogen-containing compounds.[14]

In this paper, we describe an investigation of the dual role of amines as both catalysts and substrates for the synthesis of diazo compounds or amides, depending on the structure of the starting amine and the 1,3-dicarbonyl compound employed. In addition, the synthetic application of this efficient transformation for the synthesis of indole-2-carboxamides is addressed.

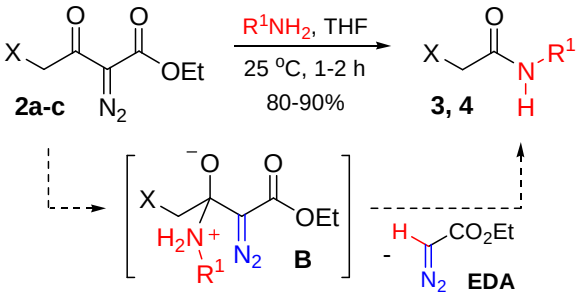


Scheme 1. Unexpected aminolysis of **2a** *versus* N-H insertion.

2. Results and discussion

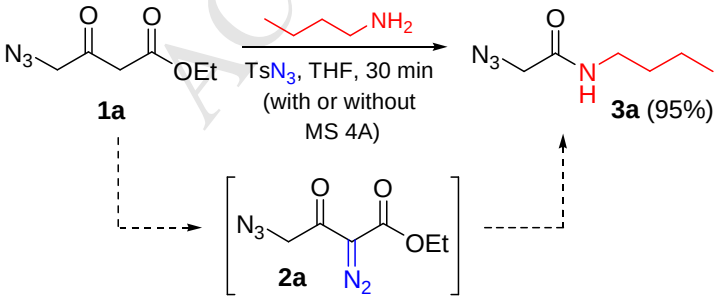
In a preliminary approach to evaluate the reactivity of α-diazo-β-keto esters toward primary amines of linear structure, it was shown that *n*-butylamine and allylamine are potent nucleophiles for the acyl cleavage of α-diazo-β-keto esters containing electron-withdrawing groups at the γ-position, such as azido (**2a**) and chloro (**2b**), leading to the corresponding amides **3** and **4** in high yields after 1-2 h at r.t. (Scheme 2). On the other hand, the unsubstituted analogue **2c** was not able to participate in a clean reaction with *n*-butylamine to give the elusive amide **3c**. Instead, a complex mixture of products was slowly formed after prolonged periods. Diazo diesters, such as dimethyl and diethyl α-diazomalonates, were even less reactive toward *n*-butylamine, being recovered intact after exposure for a few days. These results indicate that the cleavage occurs preferentially with more reactive β-keto esters, where the presence of an electron-withdrawing group at the adjacent γ-position activates the electrophilic carbonyl center for the nucleophilic attack of the amines under

study. The proposed intermediate **B** would undergo intramolecular proton transfer and eventually expels ethyl diazoacetate (EDA), which can be detected by NMR analysis of the crude reaction but is ultimately destroyed in the work-up and purification stages (Scheme 2). Besides the simplicity, this transformation is carried out under mild conditions to give amides in high chemical yields.



Scheme 2. Aminolysis of diazo esters **2**.

The aminolysis of α-diazo-β-keto esters **2** was highly efficient in terms of producing amides **3** and **4**. However, it would be more synthetically attractive if the diazo function could be generated *in situ* from the 1,3-dicarbonyl compounds **1** in a one-pot process, instead of first preparing the α-diazo-β-keto esters **2** and then transforming them to the desired amides **3** and **4**. We recently developed a mild method to prepare α-diazo carbonyl compounds through the diazo transfer reaction starting from 1,3-dicarbonyl compounds **1**. This procedure involves the use of a diazo transfer agent (such as TsN_3) and a heterogeneous base (such as molecular sieves - MS) in THF as the solvent.[9] Because the heterogeneous conditions were compatible with the aminolysis reaction, we tested the MS-catalyzed diazo transfer reaction in the presence of *n*-butylamine to verify whether the preformed diazo product **2a** participates in subsequent amine-mediated transformations (Scheme 3).



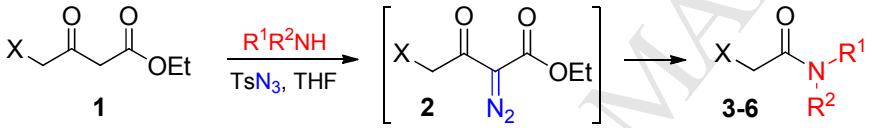
Scheme 3. Domino diazo transfer/aminolysis of keto ester **1a**.

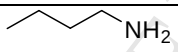
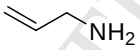
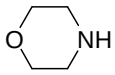
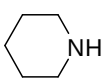
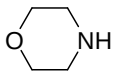
Indeed, the expected amide **3a** was obtained in high yield, but the time required to achieve this transformation was exceedingly low (30 min) compared to the MS-catalyzed diazo transfer (26 h).[9] Clearly, the presence of the added amine was crucial not only as a nucleophile for the aminolysis of the diazo intermediate **2a** in the second step, but also as a basic catalyst for the initial formation of **2a** through the diazo transfer reaction from **1a**. This hypothesis was confirmed by running a similar reaction, but in the absence of MS, wherein the expected amide **3** was obtained in comparable yield and time (Scheme 3).

This domino diazo transfer/aminolysis process was extended to other substrates, including β-keto esters and primary as well as cyclic secondary amines (Table 1). The results for the primary amines tested (*n*-butyl and allyl) were similar and led to the corresponding α-azido acetamides **3a** and **4a** in excellent yields (Table 1, entries 1 and 2) after a simple work-up consisting of triturating the crude product with a combination of ethyl ether and hexane to separate the solid tosylamide that is formed as a byproduct.

Table 1

Amine-mediated diazo transfer reaction *versus* domino diazo transfer/aminolysis.



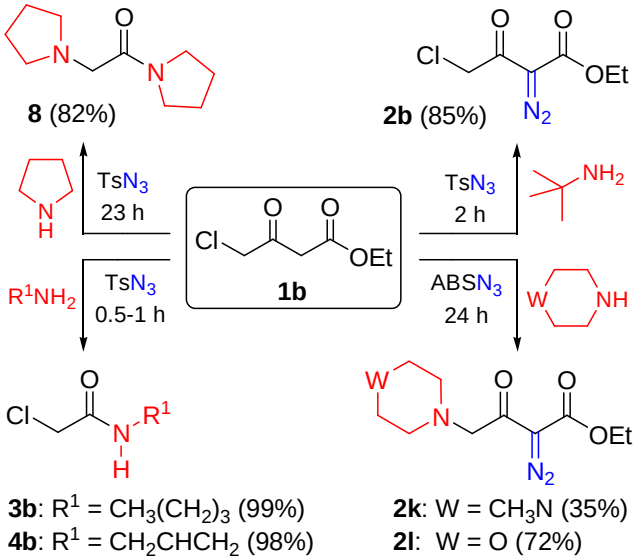
#	1	X	R^1R^2NH	Time (h)	Product	Yield (%)[a]
1	**a**	N_3		0.5	**3a**	95
2	**a**	N_3		0.5	**4a**	94
3	**a**	N_3		29	**5a**	95
4	**a**	N_3		26	**6a**	87
5	**a**	N_3		24	**2a**	80
6	**c**	H		3	**5c**	85
7	**c**	H		13	**2c**	89
8	**c**	H		16	**2c**	91

[a] Isolated yields.

On the other hand, the outcome of the reaction involving cyclic secondary amines and β-keto esters was not as predictable and was dependent on the structure of the reactants involved, providing either the expected amides **5** and **6**, through the domino diazo transfer/aminolysis process, or the diazo intermediate **2** (Table 1, entries 3-8). For instance, pyrrolidine was sufficiently basic and nucleophilic to give the corresponding tertiary amides **5a** and **5c**, even in the case of the less reactive γ-unsubstituted β-keto ester **1c** (Table 1, entries 3 and 6). Likewise, piperidine was able to participate as a nucleophile in the domino sequence to give amide **6a** when the azido-substituted 1,3-dicarbonyl compound **1a** was used as the precursor (entry 4). However, when the β-keto ester **1c** was employed as the starting material, the γ-unsubstituted α-diazo-β-keto ester **2c** was isolated as the sole product, with no trace of the elusive amide **6c** (entry 7). Moreover, morpholine was not sufficiently nucleophilic under the conditions tested and only the corresponding α-diazo-β-keto esters **2a** and **2c** were isolated from the starting β-keto esters **1a** and **1c** (respectively, entries 5 and 8).

In the case of the γ-chloro-β-keto ester **1b**, the reactions with a variety of amines led to interesting results due to the presence of an additional electrophilic center at the γ-position, which allowed further *in situ* transformations through chlorine displacement by the amine, besides the diazo transfer and aminolysis (Scheme 4). Therefore, the treatment of the γ-chloro-β-keto ester **1b** with TsN_3 and 2 equiv of pyrrolidine furnished the *bis*-adduct **8**, which might come from a domino process starting with the diazo transfer reaction generating **2b** followed by chloro displacement and aminolysis (not necessarily in this order). On the other hand, the α-chloro acetamides **3b** and **4b** were the exclusive products originating from the primary linear amines tested (*n*-butylamine and allylamine), in which the diazo transfer/aminolysis sequence occurred while the halogen group remained intact. The less reactive amines, namely, *N*-methylpiperazine and morpholine, were also able to catalyze the diazo transfer reaction, although the subsequent aminolysis of the diazo intermediate **2b** was not observed. Instead, the amines were incorporated in the final product through the displacement of the γ-chloro group, which ultimately furnished the corresponding γ-amino-α-diazo-β-keto esters **2k** and **2l** from a multicomponent-type transformation. For these particular transformations, the best results were observed by replacing TsN_3 with 4-acetamidobenzenesulfonyl azide [$ABSN_3$], which is considered a safer diazo transfer agent.[7a]

A distinct behavior was observed for the weakly nucleophilic *t*-$BuNH_2$, which was able to cleanly catalyze the diazo transfer reaction to γ-chloro-β-keto ester **1b** in the presence of TsN_3 to give the γ-chloro-α-diazo-β-keto ester **2b** as the only product detected, with no further transformation (e.g., aminolysis or chloro displacement). The preparation of γ-halo-α-diazo-β-keto esters, such as **2b**, is of particular interest due to their importance as building blocks for the synthesis of a variety of multifunctionalized compounds.[10a,15]



Scheme 4. Amine-mediated diazo transfer reaction to γ-chloro-β-keto ester **1b** *versus* domino diazo transfer/aminolysis with or without nucleophilic displacement.

Because the use of *t*-BuNH$_2$ under mild conditions allowed simple access to the α-diazo carbonyl compound **2b** in high yield, it appeared that this simple protocol might be suitable for the synthesis of diverse α-diazo carbonyl compounds. Therefore, representative 1,3-dicarbonyl compounds **1** (β-keto esters, malonates, 1,3-diketones) were screened in the *t*-BuNH$_2$-catalyzed diazo transfer reaction using TsN$_3$ as the diazo transfer reagent (Table 2, method A). Good yields and short reaction times were obtained in most cases. The exception was malonate **1f**, for which the conversion to the corresponding diazo diester **2f** was slower than in the case of the 1,3-dicarbonyl compounds **1** tested, although the yield was similar. Remarkably, the presence of reactive functional groups, including azido, chloro, and nitro groups is well tolerated (Table 2, products **2a**, **2b**, **2e**). The catalytic nature of *t*-BuNH$_2$ was attested by running a reaction with 0.25 equiv of *t*-BuNH$_2$ under identical conditions to give the expected diazo compound **2b**, although the reaction rate was considerably diminished (with a conversion of 55% after 2 h) compared to the conditions generally applied (i.e., 1.0-1.1 equiv base).

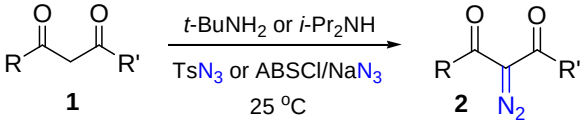
It is also possible to replace the diazo transfer reagent (TsN$_3$ with ABSN$_3$; product **2b**) and the amine catalyst (*t*-BuNH$_2$ with *i*-Pr$_2$NH; product **2c**) without a significant reduction in the reaction rate or yield. In all cases, the fast and high-yield preparation of α-diazo carbonyl compounds **2a-h** using *tert*-butylamine was found to be much more efficient than the method employing molecular sieves previously described by our group.[9]

Motivated by these results, we envisioned that the procedure for the diazo transfer reaction using *t*-BuNH$_2$ as the catalyst could be adapted to a more environmentally benign protocol if the potentially explosive TsN$_3$ and the harmful THF were replaced by a safer diazo transfer

reagent and less toxic aqueous solvent. In this regard, the *in situ* generation of the diazo transfer reagent in an aqueous environment seemed not only promising but also feasible.

Table 2

Yields for the *t*-$BuNH_2$-catalyzed diazo transfer reaction with TsN_3 or ABSCl/NaN_3.



Product	R	R'	Method A[a] [Time (h)]	Method B[a] [Time (h)]
2a	N_3CH_2	EtO	88 [1]	[b]
2b	$ClCH_2$	EtO	85 [2]	78 [2]
			75 [3][c]	
2c	CH_3	EtO	90 [1]	65 [4]
			86 [2][d]	
2d	CH_3	MeO	92 [1]	-
2e	4-$NO_2C_6H_4$	EtO	85 [0.5]	-
2f	MeO	MeO	87 [16]	57 [24]
				72 [24][e]
2g	BnO	BnO	-	77 [24]
				92 [24][f]
2h	$OC(CH_3)_2O$		-	40 [2]
2i	$CH_2C(CH_3)_2CH_2$		75 [1]	76 [3]
				70 [2][f]
2j	CH_3	CH_3	82 [0.5]	61 [2]

[a] Method A: TsN_3/*t*-$BuNH_2$/THF; Method B: ABSCl/NaN_3/*t*-$BuNH_2$/BTEAC/acetone/H_2O.

[b] Azido-substituted diazo ester **2a** was prepared directly from chloro-substituted keto ester **1b** by adapting method B to a one-pot procedure (see Scheme 6).

[c] TsN_3 was replaced with $ABSN_3$ (4-acetamidobenzenesulfonyl azide) as the diazo transfer reagent.

[d] *t*-$BuNH_2$ was replaced with *i*-Pr_2NH as the base.

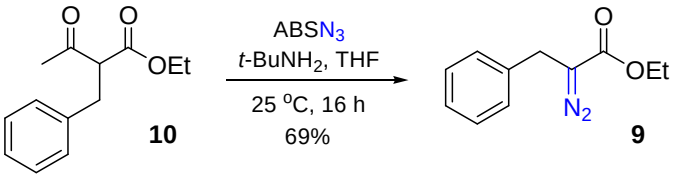
[e] Reaction was carried out without BTEAC.

[f] *t*-$BuNH_2$/BTEAC was replaced with *i*-Pr_2NH/*β*-CD as the base/additive combination.

Treating representative 1,3-dicarbonyl compounds **1** with a combination of 4-acetamidobenzenesulfonyl chloride [ABSCl], NaN_3 and a phase transfer agent (benzyltriethylammonium chloride [BTEAC]) in aqueous acetone led to the expected *α*-diazo

carbonyl product in good-to-high yields, usually after a few hours (Table 2, method B). As in the case of method A, slower reaction rates were observed for the malonate derivatives (products **2f**, **2g**). In one particular case (product **2f**), the presence of BTEAC had a negative effect on the reaction rate and better results were obtained without this additive. In a few instances, another combination of catalyst (*i*-Pr_2NH) and additive (β-cyclodextrin [β-CD]) was found to be more efficient than or at least of similar applicability as *t*-$BuNH_2$/BTEAC (products **2g**, **2i**).

As an additional feature of this straightforward method for the diazo transfer reaction, it was possible to prepare the donor-acceptor[16] α-diazo ester **9** through the acyl cleavage of the α-substituted β-keto ester **10** (Scheme 5).

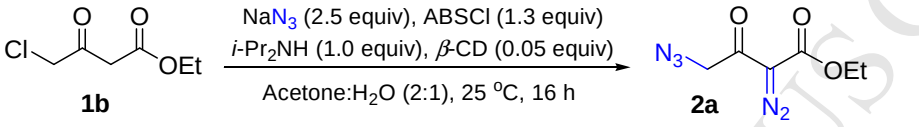


Scheme 5. Synthesis of donor-acceptor α-diazo ester **9**.

Besides being applicable to a variety of 1,3-dicarbonyl compounds **1**, this simple method for the preparation of α-diazo carbonyl compounds in aqueous medium was also practical in terms of work-up. This consisted of evaporating the volatiles and triturating the crude product with a combination of ethyl ether and hexane followed by separating out the solid sulfonamide byproduct, which provides high-quality α-diazo carbonyl compounds with no additional purification stages. It is also worth noting that despite the higher yields and shorter reaction times observed for method A, the one-pot condition described in method B is not only greener but also more practical due to the use of an aqueous medium and the *in situ* generation of the diazo transfer reagent (dispensing with the need for its previous preparation), thus reducing the amount of waste generated.

We have previously demonstrated the versatility of γ-azido-α-diazo-β-keto ester **2a** as a synthetic building block.[10] However, its preparation involves either a three-step procedure with the intermediacy of a potentially toxic diazo mercurial[10d] or an interchangeable two-step protocol starting with **1b**, consisting of an MS-catalyzed diazo transfer reaction and S_N2-type displacement.[9] In order to combine the practicability of generating the diazo transfer reagent *in situ*[7b,12b] with the introduction of the azido group through chloro displacement by the azide anion, we designed a one-pot process to prepare the γ-azido-α-diazo-β-keto ester **2a** from the γ-chloro-β-keto ester **1b** using commercially available reagents and without the isolation of intermediates (Scheme 6). It is worth mentioning the dual role of NaN_3, which acts as the

source of the diazo transfer reagent (through the *in situ* formation of $ABSN_3$ from ABSCl) and also as the nucleophile that displaces the chlorine ion at the γ-position. Thus, different amines, additives, and solvents in a variety of stoichiometric amounts of reagents were fine-tuned to find the best conditions to prepare the γ-azido-α-diazo-β-keto ester **2a** on a preparative scale. For the 1-mmol scale, the use of *t*-$BuNH_2$ combined with BTEAC was effective as expected, but the yield dropped considerably when the reaction was scaled up to 3 mmol. After extensive evaluation, the most reliable protocol for the 3-mmol scale was found to be a combination of *i*-Pr_2NH and β-CD in aqueous acetone. With a slight excess of ABSCl as the precursor of the diazo transfer reagent, high-quality **2a** was obtained in reproducible yields (up to 80%) without the need for a chromatography stage (Scheme 6).



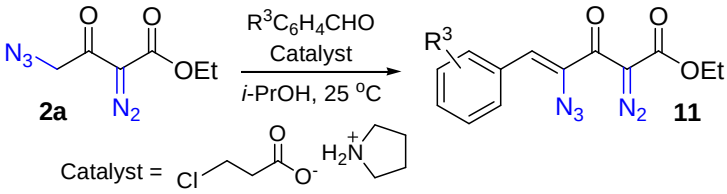
Scheme 6. One-pot preparation of azido diazo ester **2a**.

The safe and practical one-pot synthesis of the γ-azido-α-diazo-β-keto ester **2a** from γ-chloro-β-keto ester **1b** allowed the full exploitation of its reactivity through the Knoevenagel-Knittel condensation toward aldehydes.[17] The original reaction of **2a** with benzaldehyde[10a] using piperidinium acetate as the promoter was modified in order to improve the reaction yield and selectivity. Thus, a variety of carboxylic acids and amines were tested as the acid-base promoters of the condensation in a number of solvents. After some experimentation, the best conditions were found to be the combination of 3-chloropropionic acid and pyrrolidine (1.5 equiv each) in isopropanol as the solvent. The use of the more nucleophilic ethanol as the solvent was deleterious due to the observed formation of ethyl α-azidocinnamate[10a] through the acyl cleavage of the preformed condensation product **11**. With this mild condition in hand, a series of representative Knoevenagel-Knittel adducts was prepared in good to high yields (Table 3).

This late functionalization of the γ-azido-α-diazo-β-keto ester **2a** was useful since the resulting unsaturated γ-azido-α-diazo-β-keto esters **11** also participated in the aminolysis reaction in the presence of a suitable amine. Accordingly, treating **11a** with *n*-butylamine cleanly furnished the corresponding α-azidocinnamamide **12a** in excellent yields (Table 4). Due to the importance of α-azidocinnamamides **12** as starting materials for imidazole-based fluorophores used in RNA imaging,[18] this transformation was further extended to other substrates and found to be wide in scope (Table 4, **12b-j**).

Table 3

Preparation of unsaturated γ-azido-α-diazo-β-keto esters **11** through Knoevenagel-Knittel condensation.

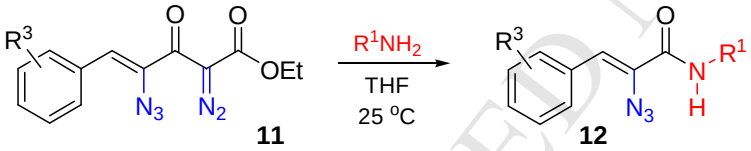


Product	R^3	Time (h)	Yield (%)[a]
11a	H	14	65
11b	4-CH_3	26	90
11c	4-CH_3O	22	75
11d	3-CH_3O	19	76
11e	4-Br	26	67

[a] Isolated yields.

Table 4

Preparation of α-azidocinnamamides **12** through the aminolysis reaction of unsaturated γ-azido-α-diazo-β-keto esters **11**.



Product	R^1	R^3	Time (h)	Yield (%)[a]
12a	$CH_3CH_2CH_2CH_2$	H	26	88
12b	$C_6H_5CH_2$	H	30	65
12c	$CH_3CH_2CH_2CH_2$	4-CH_3	22	90
12d	CH_2=$CHCH_2$	4-CH_3	2	76
12e	$CH_3CH_2CH_2CH_2$	4-CH_3O	9	94
12f	CH_2=$CHCH_2$	4-CH_3O	2	85
12g	$C_6H_5CH_2$	4-CH_3O	50	66
12h	CH_2=$CHCH_2$	3-CH_3O	1	87
12i	$CH_3CH_2CH_2CH_2$	4-Br	2	92
12j	$C_6H_5CH_2$	4-Br	35	91

[a] Isolated yields.

α-Azidocinnamic esters are well-known precursors for indole-2-carboxylates. These can be obtained either by thermally-induced cyclization with the intermediacy of vinyl nitrene-azirine

species (the Hemetsberger indole synthesis),[19] or through the milder rhodium-catalyzed generation of a metallo-nitrenoid intermediate and subsequent intramolecular C-H insertion followed by rearomatization.[20] While the importance of the related indole-2-carboxamides **13** has been widely recognized in the medicinal area[21] (Figure 1), the synthesis of indole-2-carboxamides **13** through the cyclization of the corresponding α-azidocinnamamides, such as **12**, has not been well documented,[22] possibly due to the absence of truly general methods for the synthesis of this class of compounds.

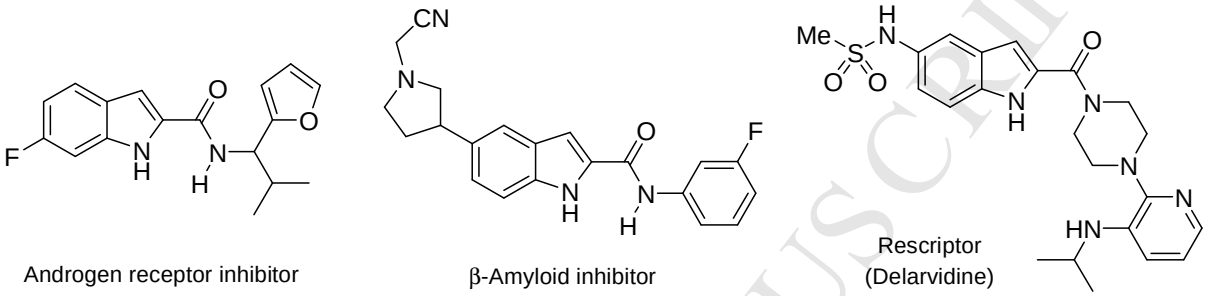


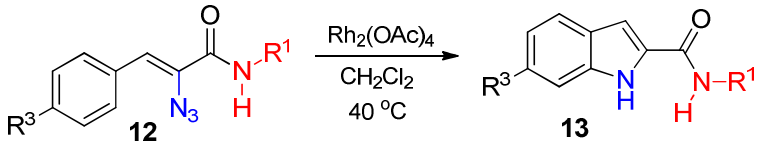
Figure 1. Selected examples for bioactive indole-2-carboxamides.

To further demonstrate the synthetic potential of α-azidocinnamamides **12** as useful building blocks, we pursued a straightforward route to indole-2-carboxamides **13** employing the known metal-catalyzed intramolecular C-H nitrene insertion of related α-azidocinnamic esters.[20] In this regard, we initially based our studies on the use of rhodium(II) perfluorobutyrate [$Rh_2(pfb)_4$] in toluene at 40 ℃, as described by Driver and c ols.[20a] However, the treatment of cinnamamide **12e** with $Rh_2(pfb)_4$ in toluene (or dichloromethane) under Driver's conditions[20a] provides only a slow conversion to the expected indoles (less than 40% after 30 h). Gratifyingly, replacing the catalyst ($Rh_2(pfb)_4$ with $Rh_2(AcO)_4$) cleanly gave indole **13b** in excellent yield[23] (Table 5).

Therefore, a representative group of α-azidocinnamamides **12** was treated with $Rh_2(AcO)_4$ (5 mol%) in CH_2Cl_2 to give the corresponding indole-2-carboxamides **13** in 93-98% yield. The reaction is very slow at room temperature, but can be dramatically improved at 40 ℃ (Table 5). It is worth noting the relevant differences between the two rhodium(II) catalysts: the use of $Rh_2(AcO)_4$ for the previous intramolecular C-H nitrene insertion of α-azidocinnamic esters did not give satisfactory results compared to the more electrophilic $Rh_2(pfb)_4$,[20] while the reverse situation was observed for the α-azidocinnamamides **12** presented herein. These results highlight the ability of each ligand to determine the course of the catalytic process involved in the generation of nitrenoid species from azides, as observed before for the intermediacy of carbenoids originated from the related diazo compounds.[24]

Table 5

Synthesis of indole-2-carboxamides **13** from α-azidocinnamamides **12** through rhodium-catalyzed intramolecular C-H nitrene insertion.



Product	R^1	R^3	Time (h)	Yield (%)[a]
13a	$CH_3CH_2CH_2CH_2$	CH_3	27	98
13b	$CH_3CH_2CH_2CH_2$	CH_3O	13	93
13c	CH_2=$CHCH_2$	CH_3O	20	96
13d	$CH_3CH_2CH_2CH_2$	Br	26	93
13e	$C_6H_5CH_2$	Br	20	94

[a] Isolated yields.

Since the reaction rate for the rhodium-catalyzed synthesis of indole-2-carboxamides **13** from α-azidocinnamamides **12** is strongly dependent on the temperature, attempts were made to adapt the Hemetsberger indole synthesis to a method using microwave irradiation in the absence of a catalyst, as reported earlier for α-azidocinnamic esters.[19d] The irradiation of **12b** in toluene at 120-130 ℃ for 5 min led to complete consumption of the starting α-azidocinnamamide **12b**, but the resulting indole-2-carboxamide **13b** was accompanied by small amounts of non-identifiable byproducts. Changing the solvent (toluene with ethanol) or running the reaction under solvent-free conditions was detrimental to the process due to the formation of complex mixtures of products. Despite the limitations observed for the microwave-assisted Hemetsberger synthesis of indoles, the very fast conversion of α-azidocinnamamides **12** to indole-2-carboxamides **13** in toluene (5 min) compared to the rhodium-catalyzed process (13 to 27 h) is encouraging and suggests that the reaction time could be considerably reduced through a fine-tuning of the reaction parameters to achieve yields and selectivity similar to those obtained under rhodium catalysis.

3. Conclusions

We have presented a general and benign approach for the preparation of α-diazo carbonyl compounds **2** through the diazo transfer reaction to 1,3-dicarbonyl compounds catalyzed by primary or secondary amines. The resulting α-diazo-β-keto esters undergo cleavage of the acyl group to give amides depending on the reaction conditions and the substrates employed. This domino diazo transfer/aminolysis process occurs under mild conditions and

the resulting amides were isolated in high yields. The use of a γ-chloro-β-keto ester allowed further *in situ* transformations through chlorine displacement by cyclic amines.

Due to their poorer nucleophilicity, the use of *tert*-butylamine and diisopropylamine did not lead to aminolysis products and thus they were successfully employed as basic catalysts for the diazo transfer reaction to give a representative group of diazo compounds. The involvement of readily available reagents, the *in situ* generation of the diazo transfer reagent in an aqueous environment, and the tolerance to a variety of functional groups, together with the simple work-up and good-to-high yields of the diazo compounds, were the main advantages of this diazo transfer reaction over the existing methods. This simple protocol allowed the development of a one-pot process for the synthesis of the multifunctionalized γ-azido-α-diazo-β-keto ester **2a** under more practical and safer conditions compared with previously reported procedures.

Subsequent organocatalyzed Knoevenagel-type condensation of **2a** with aldehydes followed by aminolysis of the resulting unsaturated γ-azido-α-diazo-β-keto esters **11** under mild conditions and in short reaction times led to a novel protocol to access the important class of α-azidocinnamamides **12** in excellent yields. Finally, the synthetic application of amides **12** as suitable precursors of indole-2-carboxamides **13** was firmly established through rhodium-catalyzed intramolecular C-H insertion, but the fast microwave-assisted cyclization in the absence of a catalyst shows potential for additional investigations to achieve improved selectivity. Due to the recognized importance of amides and diazo compounds, further studies are in progress to apply the methods developed herein for the synthesis of biologically relevant targets.

4. Experimental section

4.1. General Experimental Methods

All chemicals were of reagent grade and were used as received. Melting points were determined using a hot plate apparatus and are uncorrected. Infrared spectra were acquired with a FT-IR spectrometer (range 4000-400 cm^{-1}) using KBr or ZnSe for solids and film for liquid samples. ^{1}H NMR spectra were recorded at 400 MHz or at 200 MHz and ^{13}C $\{^{1}H\}$ NMR spectra (fully decoupled) were recorded at 100 MHz or at 50 MHz. Splitting patterns are designated as s (singlet), brs (broad singlet), d (doublet), dd (doublet of doublet), ddt (doublet of doublet of triplet), t (triplet), tt (triplet of triplet), q (quartet), qt (quintet), st (sextet), m (multiplet). Coupling constants (*J*) are measured in Hertz (Hz). Chemical shifts were recorded in parts per million (ppm, δ) relative to solvent ($CDCl_3$ at 7.26 ppm or DMSO-d_6 at 2.48 ppm for ^{1}H NMR, and $CDCl_3$ at 77.16 ppm or DMSO-d_6 at 39.52 ppm for ^{13}C NMR) as the internal standard. Column chromatography was performed using silica gel (70-230 mesh)

and hexane/ethyl acetate as the eluent. TLC analysis was performed in silica gel plates. The ESI-QTOF mass spectrometer was operated in the positive ion mode at 4.5 kV and at a desolvation temperature of 180 ℃. The standard ele ctrospray ion (ESI) source was used to generate the ions. The instrument was calibrated in the range *m/z* 50-3000 using a calibration standard (low concentration tuning mix solution) and data were processed with the aid of computer software.

Caution: Organic azides are potentially explosive substances that can decompose with the input of energy from external sources (light, heat, pressure etc).

4.2. Typical procedure for the amine-mediated domino diazo transfer/aminolysis

To a solution of the corresponding *β*-keto ester **1** (1.0 mmol) and TsN_3 (197 mg, 1.0 mmol) in THF (2.0 mL) under stirring at 25 ℃ was added the amine (1.1 mmol). Then the reaction mixture was stirred at room temperature until consumption of the starting material (monitored by TLC: 30 min to 29 h, see Table 1 and Scheme 4). Next, the mixture was diluted in 5 mL of CH_2Cl_2 and concentrated under reduced pressure. After complete removal of the solvent, the residue was triturated in ethyl ether and the resulting mixture was again concentrated under reduced pressure. The final solid residue was repeatedly triturated with hexane (for amides **3** and **4**) or a 9:1 hexane/CH_2Cl_2 mixture (for amides **5** and **6**) to separate out the insoluble $TsNH_2$ by decantation. The resulting supernatants were filtered and concentrated under reduced pressure to give the known amides[25] **3-6** as oils with high degree of purity. Alternatively, further purification through column chromatography on silica gel using gradient mixtures of hexane/EtOAc as eluent was employed to furnish pure products in 80-99% yield.

*4.3. Preparation of 1-(2-pyrrolidinoacetyl)pyrrolidine (**8**) from the pyrrolidine-mediated domino diazo transfer/chloro displacement/aminolysis*

To a solution of 4-chloroacetoacetate (**1b**, 164 mg, 1.0 mmol) and TsN_3 (197 mg, 1.0 mmol) in THF (2.0 mL) under stirring at 25 ℃ was added p yrrolidine (150 mg, 2.1 mmol). Then the reaction mixture was stirred at room temperature for 23 h. The final mixture was diluted with CH_2Cl_2 and the organic extract was washed with 0.5 M NaOH and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified through column chromatography on silica gel (8:2 hexane/EtOAc) to give the corresponding product **8** (149 mg, 82%) as an oil; IR (neat) ν_{max}/cm^{-1}: 3468, 2967, 2873, 2792, 1643, 1453, 1192, 1159; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.40 (q, J = 6.5 Hz, 4H), 3.24 (s, 2H), 2.62-2.60 (m, 4H), 1.92-1.85 (m, 2H), 1.82-1.72 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 58.2, 54.1 (2 × CH_2), 45.9, 45.6, 26.0, 24.0, 23.6 (2 × CH_2); HRMS (ESI+) calcd for $C_{10}H_{19}N_2O^+$ $[M+H]^+$: 183.1492, found: 183.1492.

4.4. Procedure for the amine-catalyzed domino diazo transfer/chloro displacement

To a solution of 4-chloroacetoacetate (**1b**, 164 mg, 1.0 mmol) and $ABSN_3$ (240 mg, 1.0 mmol) in THF (3.0 mL) under stirring at 25 ℃ was added the cyclic amine (2.5 mmol), then the reaction mixture was stirred at room temperature for 24 h. Next, the mixture was diluted in 5 mL of EtOAc and the organic extract was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. After complete removal of the solvent, the residue was triturated in ethyl ether and the resulting mixture was again concentrated under reduced pressure. The final solid residue was repeatedly triturated with 9:1 hexane/CH_2Cl_2 mixture to separate out the insoluble $ABSNH_2$ by decantation. The resulting supernatants were filtered and concentrated under reduced pressure and the final residue was purified through column chromatography on alumina (8:2 hexane/EtOAc) for **2k** and silica gel (8:2 hexane/EtOAc) for **2l** to give the corresponding diazo compounds **2k** (89 mg, 35%) and **2l** (173 mg, 72%) as oils.

*4.4.1. Ethyl 2-diazo-4-(4-methylpiperazin-1-yl)-3-oxobutanoate (**2k**)*

IR (neat) ν_{max}/cm^{-1}: 2978, 2939, 2800, 2136, 1715, 1666, 1456, 1373, 1305, 1222, 1012, 744; ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.26 (q, J = 7.0 Hz, 2H), 3.63 (s, 2H), 2.60-2.55 (m, 4H), 2.48-2.42 (m, 4H), 2.24 (s, 3H), 1.28 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.9, 161.1, 64.4, 61.4, 54.7 (2 × CH_2), 53.0 (2 × CH_2), 45.7, 14.2 (C=N_2 is absent); HRMS (ESI+) calcd for $C_{11}H_{18}N_4O_3^+$ $[M+H]^+$: 255.1452, found: 255.1451.

*4.4.2. Ethyl 2-diazo-4-(4-morpholinyl)-3-oxobutanoate (**2l**)*

IR (neat) ν_{max}/cm^{-1}: 2961, 2910, 2853, 2134, 1714, 1665, 1305, 1220, 1116, 866, 745; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.28 (q, J = 7.2 Hz, 2H) 3.74 (t, J = 4.5 Hz, 4H), 3.66 (s, 2H), 2.59 (t, J = 4.5 Hz, 4H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 188.8, 161.0, 66.8 (2 × CH_2), 64.8, 61.4, 53.6 (2 × CH_2), 14.2 (C=N_2 is absent); HRMS (ESI+) calcd for $C_{10}H_{15}N_3O_4^+$ $[M+H]^+$: 242.1135, found: 242.1137.

4.5. Typical procedure for the t-BuNH_2-catalyzed diazo transfer reaction with TsN_3 (Method A)

To a solution of the corresponding 1,3-dicarbonyl compound **1** (1.0 mmol) and TsN_3 (197 mg, 1.0 mmol) in THF (2.0 mL) under stirring at 25 ℃ was added *t*-BuNH_2 (80 mg, 1.1 mmol). Then the reaction mixture was stirred at room temperature until consumption of the starting material (monitored by TLC: 30 min to 16 h, see Table 2). Next, the mixture was diluted in 5 mL of CH_2Cl_2 and concentrated under reduced pressure. After complete removal of the solvent, the residue was triturated in ethyl ether and the resulting mixture was again

concentrated under reduced pressure. The final solid residue was repeatedly triturated with hexane to separate out the insoluble $TsNH_2$ by decantation. The resulting supernatants were filtered and concentrated under reduced pressure to give diazo compounds[9,10d,26] **2** as oils with high degree of purity in 75-92% yield.

4.6. Typical procedure for the amine-catalyzed diazo transfer reaction under aqueous medium through the in situ generation of $ABSN_3$ (Method B)

To a solution of the corresponding 1,3-dicarbonyl compound **1** (1.0 mmol) and ABSCl (304 mg, 1.3 mmol) in acetone (2.0 mL) under stirring at 0-5 ℃ was added a cold solution of NaN_3 (71 mg, 1.1 mmol) in H_2O (1.0 mL) followed by BTEAC (45 mg, 0.20 mmol) and *t*-$BuNH_2$ (73 mg, 1.0 mmol) [or β-CD (57 mg, 0.05 mmol and *i*-Pr_2NH (101 mg, 1.0 mmol); see Table 2]. Then the reaction mixture was stirred at room temperature until consumption of the starting material (monitored by TLC: 2 to 24 h, see Table 2). Next, the mixture was diluted in 5 mL of EtOAc and the organic extract was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. After complete removal of the solvent, the residue was triturated in ethyl ether and the resulting mixture was again concentrated under reduced pressure. The final solid residue was repeatedly triturated with hexane to separate out the insoluble $ABSNH_2$ by decantation. The resulting supernatants were filtered and concentrated under reduced pressure to give diazo compounds[9,10d,26] **2** as oils with high degree of purity in 40-92% yield.

*4.7. Preparation of ethyl 2-diazohydrocinnamate (**9**) through the t-$BuNH_2$-catalyzed diazo transfer reaction with $ABSN_3$*

To a solution of α-benzyl-β-keto ester **10** (220 mg, 1.0 mmol) and $ABSN_3$ (240 mg, 1.0 mmol) in THF (2.0 mL) under stirring at 25 ℃ was added *t*-$BuNH_2$ (73 mg, 1.0 mmol). After 1 h, another portion of $ABSN_3$ (120 mg, 0.5 mmol) and *t*-$BuNH_2$ (36 mg, 0.5 mmol) was added to the reaction mixture and the stirring was continued at room temperature until consumption of the starting material (monitored by TLC: 16 h). Next, the mixture was diluted in 5 mL of EtOAc and the organic extract was washed with 1 M NaOH, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified through column chromatography on silica gel (8:2 hexane/EtOAc) to give ethyl 2-diazohydrocinnamate[27] (**9**) as an oil (140 mg, 69%) with high degree of purity. IR (neat) ν_{max}/cm^{-1}: 3064, 3031, 2982, 2935, 2085, 1742, 1693, 1263, 1105, 738, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.21 (m, 5H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.62 (s, 2H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 137.2, 128.7 (2 × CH), 128.3 (2 × CH), 127.0, 60.8, 29.3, 14.4 ($C=N_2$ is absent); HRMS (ESI+) calcd for $C_{11}H_{12}N_2O_2^+$ $[M+Na]^+$: 227.0791, found: 227.0790.

*4.8. i-Pr_2NH-mediated one-pot preparation of ethyl 4-azido-2-diazo-3-oxobutanoate (**2a**) from ethyl 4-chloroacetoacetate (**1b**) under aqueous medium*

To a solution of ethyl 4-chloroacetoacetate (**1b**, 494 mg, 3.0 mmol) and ABSCl (911 mg, 3.9 mmol) in acetone (6.0 mL) under stirring at 0-5 ℃ was added a cold solution of NaN_3 (487 mg, 7.5 mmol) in H_2O (3.0 mL) followed by β-CD (170 mg, 0.15 mmol) and *i*-Pr_2NH (303 mg, 3.0 mmol). Then the reaction mixture was stirred at room temperature for 16 h. Next, the mixture was diluted in 15 mL of EtOAc and the organic extract was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. After complete removal of the solvent, the residue was triturated in ethyl ether and the resulting mixture was again concentrated under reduced pressure. The final solid residue was repeatedly triturated with hexane to separate out the insoluble $ABSNH_2$ by decantation. The resulting supernatants were filtered and concentrated under reduced pressure to give 4-azido-2-diazo-3-oxobutanoate (**2a**) as an oil (464 mg, 78%) with high degree of purity.

4.9. Typical procedure for the Knoevenagel-Knittel condensation

To a mixture of pyrrolidine (212 mg, 3.0 mmol) and 3-chloropropionic acid (325 mg, 3.0 mmol) in isopropanol (4.0 mL) under stirring at 25 ℃ was added ethyl 4-azido-2-diazoacetoacetate (**2a**, 394 mg, 2.0 mmol) followed by the aromatic aldehyde (2.5 mmol). Then the reaction mixture was stirred at room temperature until consumption of the starting material (monitored by TLC: 14 to 26 h, see Table 3). The final mixture was diluted with CH_2Cl_2 and the organic extract was washed with 0.1 M HCl, satd $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified through column chromatography on silica gel using gradient mixtures of hexane/EtOAc as eluent to give the corresponding condensation products **11** as oils.

*4.9.1. Ethyl (Z)-4-azido-2-diazo-3-oxo-5-phenylpent-4-enoate (**11a**)*[10a]

Yield 65% (371 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, 2H, *J* = 7.6 Hz), 7.42-7.32 (m, 3H), 6.45 (s, 1H), 4.31 (q, 2H, *J* = 7.2 Hz), 1.31 (t, 3H, *J* = 7.2 Hz).

*4.9.2. Ethyl (Z)-4-azido-2-diazo-5-(4-methylphenyl)-3-oxopent-4-enoate (**11b**)*

Yield 90% (539 mg); IR (neat) ν_{max}/cm^{-1}: 2980, 2115, 1722, 1620, 1603, 1370, 1325, 1300, 1099, 746; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, 2H, *J* = 8.0 Hz), 7.19 (d, 2H, *J* = 8.0 Hz), 6.45 (s, 1H), 4.31 (q, 2H, *J* = 7.2 Hz), 2.37 (s, 3H), 1.30 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.8, 160.8, 140.1, 130.6 (2 × CH), 130.2, 130.1, 129.4 (2 × CH), 127.0, 62.1, 21.6, 14.4 (C=N_2 is absent); HRMS (ESI+) calcd for $C_{14}H_{13}N_5O_3Na^+$ $[M+Na]^+$: 322.0911, found: 322.0909.

*4.9.3. Ethyl (Z)-4-azido-2-diazo-5-(4-methoxyphenyl)-3-oxopent-4-enoate (**11c**)*

Yield 75% (473 mg); IR (neat) ν_{max}/cm^{-1}: 2980, 2838, 2134, 2115, 1722, 1597, 1509, 1304, 1257, 1177, 831; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, 2H, *J* = 8.8 Hz), 6.91 (d, 2H, *J* = 8.8 Hz), 6.46 (s, 1H), 4.30 (q, 2H, *J* = 7.0 Hz), 3.84 (s, 3H), 1.30 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.4, 160.6 (2 × C), 132.3 (2 × CH), 128.7, 127.0, 125.6, 113.8 (2 × CH), 61.8, 55.1, 14.1 (C=N_2 is absent); HRMS (ESI+) calcd for $C_{14}H_{13}N_5O_4Na^+$ $[M+Na]^+$: 338.08598, found: 338.08596.

*4.9.4. Ethyl (Z)-4-azido-2-diazo-5-(3-methoxyphenyl)-3-oxopent-4-enoate (**11d**)*

Yield 76% (478 mg); IR (neat) ν_{max}/cm^{-1}: 2982, 2836, 2138, 2116, 1726, 1620, 1370, 1304, 1105, 741, 688; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, 1H, *J* = 1.6 Hz), 7.30-7.26 (m, 2H), 6.90-6.86 (m, 1H), 6.39 (s, 1H), 4.29 (q, 2H, *J* = 7.2 Hz), 3.81 (s, 3H), 1.28 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.8, 160.5, 159.5, 134.1, 131.0, 129.4, 126.2, 123.3, 115.4, 115.3, 62.1, 55.3, 14.3 (C=N_2 is absent); HRMS (ESI+) calcd for $C_{14}H_{13}N_5O_4Na^+$ $[M+Na]^+$: 338.0860, found: 338.0858.

*4.9.5. Ethyl (Z)-4-azido-5-(4-bromophenyl)-2-diazo-3-oxopent-4-enoate (**11e**)*

Yield 67% (488 mg); IR (neat) ν_{max}/cm^{-1}: 2980, 2118, 1724, 1616, 1582, 1484, 1370, 1300, 1096, 1010; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, 2H, *J* = 8.5 Hz), 7.50 (d, 2H, *J* = 8.5 Hz), 6.35 (s, 1H), 4.31 (q, 2H, *J* = 7.2 Hz), 1.30 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.8, 160.5, 132.0 (2 × CH), 131.9, 131.8 (2 × CH), 131.5, 124.9, 123.8, 62.2, 14.4 (C=N_2 is absent); HRMS (ESI+) calcd for $C_{13}H_{10}BrN_5O_3Na^+$ $[M+Na]^+$: 385.9859, found: 385.9857.

*4.10. Typical procedure for the aminolysis of Knoevenagel-Knittel adducts **11***

To a solution of the Knoevenagel-Knittel adduct **11** (1.0 mmol) in THF (2.0 mL) under stirring at 25 ℃ was added the corresponding amine (1.2 mmol). Then the reaction mixture was stirred at room temperature until consumption of the starting material (monitored by TLC: 1 to 50 h, see Table 4). The final mixture was diluted with CH_2Cl_2 and the organic extract was washed with 0.1 M HCl and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified through column chromatography on silica gel (85:15 hexane/EtOAc) to give the corresponding acrylamides **12** as crystalline yellow solids.

*4.10.1. (Z)-2-Azido-N-butyl-3-phenylacrylamide (**12a**)*

Yield 88% (215 mg); mp 78-79 ℃; IR (neat) ν_{max}/cm^{-1}: 3319, 2957, 2872, 2114, 1636, 1613, 1537, 1371, 690; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, 2H, *J* = 7.5 Hz), 7.38 (t, 2H, *J* = 7.5 Hz), 7.30 (t, 1H, *J* = 7.5 Hz), 6.76 (s, 1H), 6.44 (br s, 1H), 3.37 (q, 2H, *J* = 7.3 Hz), 1.57 (qt, 2H, *J* = 7.3 Hz), 1.39 (st, 2H, *J* = 7.3 Hz), 0.95 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2, 133.5, 132.9, 129.5 (2 × CH), 128.6, 128.4 (2 × CH), 121.3, 39.8, 31.5, 20.1, 13.7; HRMS (ESI+) calcd for $C_{13}H_{16}N_4ONa^+$ $[M+Na]^+$: 267.1216, found: 267.1218.

*4.10.2. (Z)-2-Azido-N-benzyl-3-phenylacrylamide (**12b**)*

Yield 65% (181 mg); mp 101-102 ℃; IR (neat) ν_{max}/cm^{-1}: 3287, 3031, 2920, 2115, 1636, 1616, 1534, 1373, 1271, 689; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, 2H, *J* = 8.0 Hz), 7.45-7.25 (m, 8H), 6.84 (s, 1H), 6.74 (br s, 1H), 4.58-4.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 163.2, 137.7, 132.9, 130.0, 129.8 (2 × CH), 129.0 (2 × CH), 128.9, 128.6 (2 × CH), 128.1 (2 × CH), 127.9, 122.2, 44.2; HRMS (ESI+) calcd for $C_{16}H_{15}N_4O^+$ $[M+H]^+$: 279.1240, found: 279.1243.

*4.10.3. (Z)-2-Azido-N-butyl-3-(4-methylphenyl)acrylamide (**12c**)*

Yield 90% (232 mg); mp 111-112 ℃; IR (neat) ν_{max}/cm^{-1}: 3312, 2964, 2931, 2868, 2116, 1634, 1612, 1533, 1323, 876, 814; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, 2H, *J* = 7.8 Hz), 7.18 (d, 2H, *J* = 7.8 Hz), 6.73 (s, 1H), 6.45 (br s, 1H), 3.36 (q, 2H, *J* = 7.4 Hz), 2.36 (s, 3H), 1.58 (qt, 2H, *J* = 7.4 Hz), 1.39 (st, 2H, *J* = 7.4 Hz), 0.95 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 138.9, 130.1, 129.6 (2 × CH), 129.4, 129.2 (2 × CH), 121.7, 39.8, 31.6, 21.4, 20.1, 13.7; HRMS (ESI+) calcd for $C_{14}H_{19}N_4O^+$ $[M+H]^+$: 259.1553, found 259.1554.

*4.10.4. (Z)-N-Allyl-2-azido-3-(4-methylphenyl)acrylamide (**12d**)*

Yield 76% (184 mg); mp 92-93 ℃; IR (neat) ν_{max}/cm^{-1}: 3426, 3292, 3045, 2920, 2114, 1636, 1614, 1533, 1369, 922, 810; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, 2H, *J* = 7.8 Hz), 7.20 (d, 2H, *J* = 7.8 Hz), 6.82 (s, 1H), 6.43 (br s, 1H), 5.90 (ddt, 1H, *J* = 6.0, 10.0, 17.2 Hz), 5.26 (dd, 1H, *J* = 1.2, 17.2 Hz, 1H), 5.20 (dd, 1H, *J* = 1.2, 10.0 Hz), 4.01 (t, 2H, *J* = 6.0 Hz), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 139.2, 133.7, 130.1, 129.7 (2 × CH), 129.6, 129.3 (2 × CH), 122.2, 117.2, 42.5, 21.5; HRMS (ESI+) calcd for $C_{13}H_{15}N_4O^+$ $[M+H]^+$: 243.1240, found 243.1241.

*4.10.5. (Z)-2-Azido-N-butyl-3-(4-methoxyphenyl)acrylamide (**12e**)*

Yield 94% (258 mg); mp 116-117 ℃; IR (neat) ν_{max}/cm^{-1}: 3272, 2958, 2932, 2871, 2121, 1636, 1616, 1540, 1509, 1265, 1177, 1032; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, 2H, *J* = 8.5 Hz,), 6.91 (d, 2H, *J* = 8.5 Hz), 6.73 (s, 1H), 6.25 (br s, 1H), 3.84 (s, 3H), 3.38 (q, 2H, *J* = 7.2 Hz), 1.62-1.54 (m, 2H), 1.41 (st, 2H, *J* = 7.5 Hz), 0.96 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4, 159.9, 131.2 (2 × CH), 128.3, 125.7, 121.4, 114.0 (2 × CH), 55.3, 39.8, 31.6, 20.1, 13.7; HRMS (ESI+) calcd for $C_{14}H_{18}N_4O_2Na^+$ $[M+Na]^+$:297.1322, found 297.1321.

*4.10.6. (Z)-N-Allyl-2-azido-3-(4-methoxyphenyl)acrylamide (**12f**)*

Yield 85% (219 mg); mp 97-98 ℃; IR (neat) ν_{max}/cm^{-1}: 3273, 2930, 2835, 2123, 1636, 1616, 1605, 1509, 1253, 1177, 1030, 830; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, 2H, *J* = 8.6 Hz, 2H), 6.92 (d, 2H, *J* = 8.6 Hz), 6.78 (s, 1H), 6.37 (br s, 1H), 5.91 (ddt, 1H, *J* = 5.6, 10.0, 17.0 Hz), 5.32-5.17 (m, 2H), 4.02 (tt, 2H, *J* = 1.5, 5.6 Hz), 3.84 (s, 3H); ^{13}C NMR (100 MHz,

$CDCl_3$): δ 160.0, 150.1, 133.8, 131.4 (2 × CH), 128.0, 125.6, 122.0, 117.2, 114.1 (2 × CH), 55.4, 42.5; HRMS (ESI+) calcd for $C_{13}H_{15}N_4O_2^+$ $[M+H]^+$: 259.1190, found 259.1186.

*4.10.7. (Z)-2-Azido-N-benzyl-3-(4-methoxyphenyl)acrylamide (**12g**)*

Yield 66% (203 mg); mp 88-89 ℃; IR (neat) ν_{max}/cm^{-1}: 3289, 2932, 2118, 1636, 1605, 1535, 1510, 1250, 1180, 1030, 830; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, 2H, *J* = 8.4 Hz), 7.40-7.30 (m, 5H), 6.91 (d, 2H, *J* = 8.4 Hz), 6.78 (s, 1H), 6.62 (br s, 1H), 4.57-4.55 (m, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 160.0, 137.8, 131.4 (2 × CH), 128.9 (2 × CH), 128.0 (2 × CH), 127.9, 127.8, 125.6, 122.0, 114.0 (2 × CH), 55.4, 44.2; HRMS (ESI+) calcd for $C_{17}H_{17}N_4O_2^+$ $[M+H]^+$: 309.1346, found 309.1345.

*4.10.8. (Z)-N-Allyl-2-azido-3-(3-methoxyphenyl)acrylamide (**12h**)*

Yield 87% (225 mg); mp 106-107 ℃; IR (neat) ν_{max}/cm^{-1}: 3410, 2955, 2840, 2121, 1654, 1618, 1534, 1258, 1047; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (t, 1H, *J* = 7.6 Hz), 7.18 (br s, 1H), 7.14 (d, 1H, *J* = 7.6 Hz), 6.88–6.84 (m, 1H), 6.77 (s, 1H), 6.50 (br s, 1H), 5.90 (ddt, 1H, *J* = 6.0, 10.0, 17.2 Hz), 5.25 (dd, 1H, *J* = 1.2, 17.2 Hz), 5.20 (dd, 1H, *J* = 1.2, 10.0 Hz), 4.02-3.98 (m, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2, 159.5, 134.2, 133.6, 130.2, 129.5, 122.4, 121.7, 117.2, 114.9, 114.6, 55.4, 42.5; HRMS (ESI+) calcd for $C_{13}H_{15}N_4O_2^+$ $[M+H]^+$: 259.1190, found 259.1187.

*4.10.9. (Z)-2-Azido-3-(4-bromophenyl)-N-butylacrylamide (**12i**)*

Yield 92% (297 mg); mp 122-124 ℃; IR (neat) ν_{max}/cm^{-1}: 3432, 3309, 2962, 2931, 2873, 2114, 1632, 1611, 1540, 1534, 1375; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.48 (m, 4H), 6.56 (s, 1H), 6.31 (br s, 1H), 3.40-3.35 (m, 2H), 1.58 (qt, 2H, *J* = 7.6 Hz), 1.40 (st, 2H, *J* = 7.6 Hz), 0.95 (t, 3H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1, 131.9, 131.6 (2 × CH), 131.1, 131.0 (2 × CH), 122.6, 119.3, 39.9, 31.5, 20.1, 13.7; HRMS (ESI+) calcd for $C_{13}H_{16}BrN_4O^+$ $[M+H]^+$: 323.0502, found 323.0501.

*4.10.10. (Z)-2-Azido-N-benzyl-3-(4-bromophenyl)acrylamide (**12j**)*

Yield 91% (325 mg); mp 133-134 ℃; IR (neat) ν_{max}/cm^{-1}: 3428, 3275, 2115, 1653, 1636, 1616, 1540, 1374; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52-7.45 (m, 4H), 7.40-7.30 (m, 5H), 6.62 (s, 1H), 4.56-4.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 137.5, 131.9, 131.7 (2 × CH), 131.1 (2 × CH), 130.8, 128.9 (2 × CH), 128.0 (2 × CH), 127.9, 122.9, 120.0, 44.2; HRMS (ESI+) calcd for $C_{16}H_{14}BrN_4O^+$ $[M+H]^+$: 357.0346, found 357.0342.

*4.11. Typical procedure for the synthesis of indoles **13***

To a solution of the α-azidocinnamamide **12** (0.3 mmol) in anhydrous CH_2Cl_2 (2.0 mL) under stirring at 25 ℃ was added $Rh_2(AcO)_4$ (7 mg, 0.015 mmol). Then the reaction mixture was stirred at 40 ℃ until consumption of the starting material (monitored by TLC: 13 to 27 h, see Table 5). The final mixture was diluted with CH_2Cl_2 and the organic extract was washed with

brine twice, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified through a pad of celite/silica gel (8:2 hexane/EtOAc for indoles **13a,d,e** and 7:3 hexane/EtOAc for **13b,c**) to give the corresponding indoles as crystalline solids.

*N-Butyl-6-methyl-1H-indole-2-carboxamide (**13a**)*

Yield 98% (68 mg); mp 196-197 ℃; IR (neat) ν_{max}/cm^{-1}: 3254, 2953, 2924, 1633, 1538, 1406, 824, 739; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.46 (br s, 1H), 7.51 (d, 1H, *J* = 8.2 Hz), 7.22 (s, 1H), 6.97 (d, 1H, *J* = 8.2 Hz), 6.77 (br s, 1H), 6.19 (br s, 1H), 3.48 (q, 2H, *J* = 7.2 Hz), 2.46 (s, 3H), 1.67-1.59 (m, 2H), 1.48-1.39 (m, 2H), 0.97 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.0, 137.0, 134.6, 130.5, 125.7, 122.8, 121.5, 111.9, 101.7, 39.6, 32.0, 22.0, 20.3, 13.9; HRMS (ESI-qTOF) Calcd for $C_{14}H_{19}N_2O^+$ $[M+H]^+$: 231.1492, found 231.1495.

*N-Butyl-6-methoxy-1H-indole-2-carboxamide (**13b**)*

Yield 93% (69 mg); mp 169-170 ℃; IR (neat) ν_{max}/cm^{-1}: 3421, 3261, 2958, 2930, 1624, 1545, 1267, 1161, 826; ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.40 (br s, 1H), 7.49 (d, 1H, *J* = 8.5 Hz), 6.86 (br s, 1H), 6.80 (dd, 1H, *J* = 2.2, 8.5 Hz), 6.76 (br s, 1H), 6.12 (br s, 1H), 3.85 (s, 3H), 3.49 (q, 2H, *J* = 7.0 Hz), 1.68-1.55 (m, 2H), 1.52-1.33 (m, 2H), 0.97 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.0, 158.3, 137.6, 130.0, 122.7, 122.1, 112.1, 102.0, 94.3, 55.6, 39.6, 32.0, 20.3, 13.9; HRMS (ESI+) calcd for $C_{14}H_{19}N_2O_2^+$ $[M+H]^+$: 247.1441, found 247.1440.

*N-Allyl-6-methoxy-1H-indole-2-carboxamide (**13c**)*

Yield 96% (66 mg); mp 180-181 ℃; IR (neat) ν_{max}/cm^{-1}: 3412, 3273, 2922, 2830, 1624, 1543, 1272, 1256, 822; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.69 (br s, 1H), 7.50 (d, 1H, *J* = 8.8 Hz), 6.87 (d, 1H, *J* = 2.0 Hz), 6.83-6.79 (m, 2H), 6.28 (br s, 1H), 6.01-5.91 (m, 1H), 5.29 (dd, 1H, *J* = 1.2, 17.2 Hz), 5.20 (dd, 1H, *J* = 1.2, 10.0 Hz), 4.15-4.11 (m, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.9, 158.4, 137.7, 134.3, 129.7, 122.8, 122.1, 116.8, 112.2, 102.5, 94.3, 55.6, 42.1; HRMS (ESI+) calcd for $C_{13}H_{15}N_2O_2^+$ $[M+H]^+$: 231.1128, found 231.1127.

*6-Bromo-N-butyl-1H-indole-2-carboxamide (**13d**)*

Yield 93% (82 mg); mp 208-209 ℃; IR (neat) ν_{max}/cm^{-1}: 3421, 3246, 2959, 2926, 2860, 1633, 1547, 1404, 1246, 824; ^{1}H NMR (400 MHz, $CDCl_3$, DMSO-d_6 as internal standard): δ 10.49 (br s, 1H), 7.13 (br s, 1H), 6.97 (d, 1H, *J* = 8.5 Hz), 6.65 (dd, 1H, *J* = 1.3, 8.5 Hz), 6.52 (br s, 1H), 2.94-2.89 (m, 2H), 1.14-1.07 (m, 2H), 0.96-0.87 (m, 2H), 0.45 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, DMSO-d_6 as internal standard): δ 160.8, 136.8, 131.9, 125.8, 122.8, 122.3, 116.5, 114.4, 102.3, 38.7, 31.1, 19.5, 13.2; HRMS (ESI+) calcd for $C_{13}H_{15}BrN_2O^+$ $[M+H]^+$: 295.0441, found 295.0441.

*N-Benzyl-6-bromo-1H-indole-2-carboxamide (**13e**)*

Yield 94% (93 mg); mp 205-206 ℃; IR (neat) ν_{max}/cm^{-1}: 3434, 3259, 2926, 1636, 1542, 1314, 1243, 734; ^{1}H NMR (200 MHz, $CDCl_3$, DMSO-d_6 as internal standard): δ 10.61 (br s, 1H),

7.87 (br s, 1H), 7.08-6.92 (m, 2H), 6.82-6.70 (m, 5H), 6.63-6.58 (m, 2H), 4.09 (d, 2H, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, DMSO-d_6 as internal standard): δ 160.8, 138.3, 136.9, 131.7, 127.9 (2 × CH), 127.2 (2 × CH), 126.6, 125.8, 122.7, 122.4, 116.6, 114.4, 103.2, 42.7; HRMS (ESI+) calcd for $C_{16}H_{13}BrN_2O^+$ $[M+H]^+$: 329.0284, found 329.0286.

Appendix A. Supplementary data

Supplementary data related to this article (NMR spectra for all novel and relevant products, and selected crystallographic data for indole **13b**) can be found at http://

Full crystallographic tables (including structure factors) for compound **13b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1540527. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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