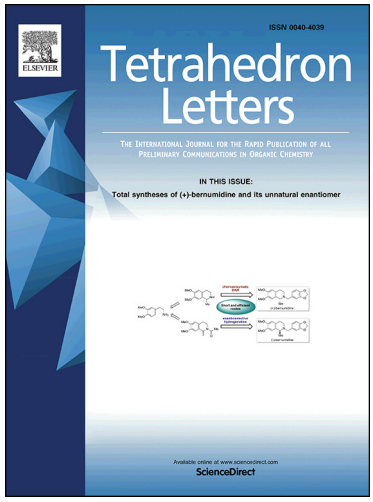

Propylphosphonic anhydride (T3P®) mediated synthesis of 3-oxoisoindoline-1-carboxamides from 2-formylbenzoic acid, amines, and isocyanides. Preparation of isoindolinone alkaloids

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Propylphosphonic anhydride (T3P®) mediated synthesis of 3-oxoisoindoline-1-carboxamides from 2-formylbenzoic acid, amines, and isocyanides. Preparation of isoindolinone alkaloids

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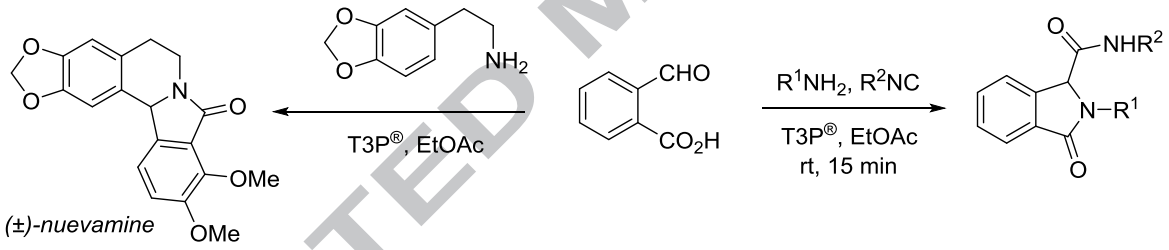
Graphical abstract



Abstract

Propylphosphonic anhydride (T3P®) was successfully applied to the synthesis of an isoindolinone library by the utilization of an Ugi four-center, three-component reaction (Ugi-4C-3CR). The use of T3P® significantly shortened the required reaction time and the corresponding products were obtained in good to high yields. Moreover, a side-reaction was observed when phenylethylamine derivatives and tryptamine were used as the amine component. The latter reaction was applied to the microwave-assisted, one-pot synthesis of the isoquinoline alkaloid (±)-nuevamine. Surprisingly, the traditional Ugi four-component reaction (Ugi-4CR) was unsuccessful in the presence of T3P®. In this case an α-amino amide was produced excluding the carboxylic acid from the multicomponent reaction.

Keywords: isoindolinones, Ugi-reaction, T3P®, natural product synthesis

Introduction

Isocyanide-based multicomponent reactions, especially the Ugi four-component reaction (Ugi-4CR), have received significant attention in synthetic organic and medicinal chemistry.[1,2] The Ugi-4CR offers an efficient and atom-economical way to construct differently functionalized molecules from readily available aldehydes, amines, carboxylic acids, and isocyanides.[3] This reaction usually takes place under mild conditions with wide functional group tolerance, but mostly with long reaction times. Multiple variations of the Ugi-reaction, such as the Ugi-4CR, several three-component Ugi reactions (Ugi-3CR), Ugi-tetrazole synthesis, oxidative Ugi reaction, and Ugi-azide repetitive processes have been applied in the generation of diverse heterocyclic libraries.[4–7]

Oxoisoindole (2,6-dihydro-2*H*-isoindole-1-one, **1**, Fig. 1) is a prevalent and important heterocyclic motif which has been widely used as a valuable building block in the pharmaceutical industry and in the synthesis of natural products.[8] For example, lenalidomide (**2**, trade name: Revlimid®) is a commercial drug for the treatment of multiple myeloma, myelodysplastic syndrome, and lymphoma.[9,10] (±)-Lennoxamine (**3**) and (±)-nuevamine (**4**) are two representative isoindolinone alkaloids which were isolated from the Chilean barberry, *Berberis darwinii*.[11]

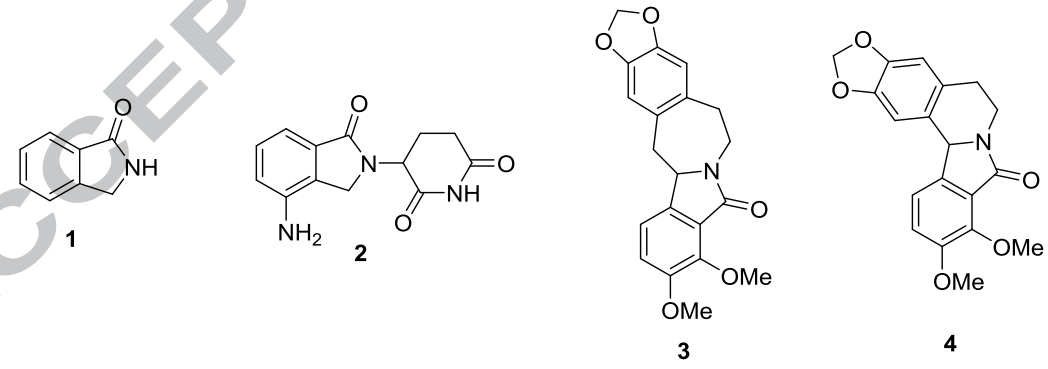
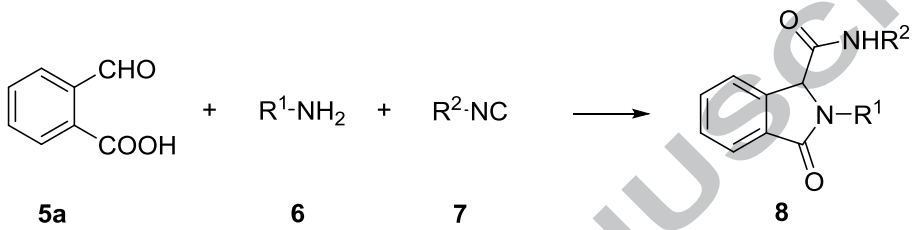


Figure 1. Structures of oxoisoindole (**1**) and selected oxoisoindole derivatives

Due to widespread interest in the isoindolinone ring system, several approaches have been developed for the synthesis of these heterocycles, but mostly utilise multistep protocols, expensive metal catalysts, halogenated solvents, or harsh reaction conditions.[12–15] The

isoindolinone scaffold can be constructed using an Ugi four-center, three-component reaction (Ugi-4C-3CR) from 2-formylbenzoic acid (**5a**), amines (**6**) and isocyanides (**7**) (Scheme 1).[16] This Ugi-4C-3CR proceeds smoothly in methanol or ethanol at room temperature and leads to the products in good yields. The only drawback of this process is the prolonged reaction time (12–24 h).[16–18] As part of our continuing interest in the development of propylphosphonic anhydride (T3P®) promoted reactions,[19–22] herein, we report a T3P®-assisted synthesis of 3-oxoisoindoline-1-carboxamides applying an Ugi-4C-3CR.

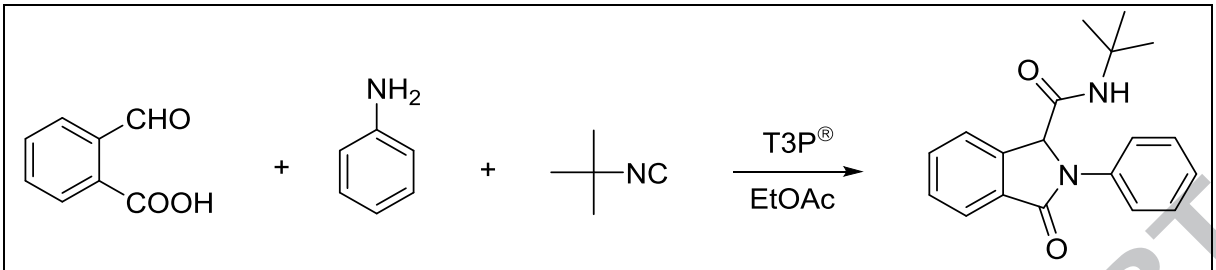


Scheme 1. Ugi-4C-3CR reaction for the synthesis of oxoisoindole derivatives

Results and Discussion

The T3P®-mediated model reaction of 2-formylbenzoic acid (**5a**), aniline (**6a**), and *tert*-butyl isocyanide (**7a**) (1 equiv. of each) was optimized by varying different experimental parameters. Initially, the effects of the reaction time and addition order of the components were investigated. It was found, that after adding all reactants, 15 min is required for the optimal yield (Table 1, entry 2). Increasing the reaction time did not improve the conversion (Table 1, entries 3–5). When *tert*-butyl isocyanide (**7a**) or T3P® was added 10 min after the rest of the reactants, the yields slightly decreased to 68% and 67%, respectively (Table 1, entries 6, 7).

Table 1. Optimization of the Ugi-4C-3CR reaction leading to oxoisoindole **8a**.



5a **6a** **7a** **8a**

Entry	Reaction time	T3P® (equiv.)	Yield[a] 8a [%]
1	5 min	1.0	71
2	15 min	1.0	74
3	1 h	1.0	73
4	2 h	1.0	70
5	4 h	1.0	75
6	15 min	1.0	68[b]
7	15 min	1.0	67[c]
8	15 min	1.0	69[d]
9	15 min	1.0	65[e]
10	15 min	1.0	66[f]
11	15 min	2.0	76
12	2 h	0.5	73
13	48 h	0.1	39
14	48 h	0	trace[g]

Reagents and conditions: **5a** (1 mmol), **6a** (1 mmol), **7a** (1 mmol), T3P® (see the appropriate column) EtOAc (3 mL), room temperature (unless otherwise indicated).
[a] Isolated yield (**8a**).
[b] *tert*-Butyl isocyanide (**7a**) added 10 min after the rest of the reactants.
[c] T3P® added 10 min after the rest of the reactants.
[d] Reaction was carried out at 70 °C.
[e] Aniline (**6a**, 1.3 equiv.).
[f] *tert*-Butyl isocyanide (**7a**, 1.3 equiv.).
[g] Detected by HPLC-MS.

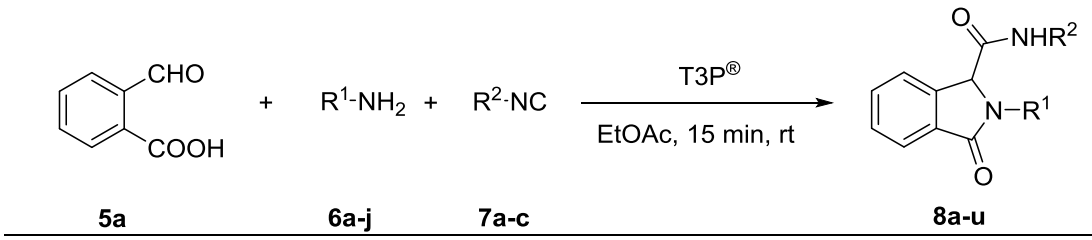
Next, the temperature and the amount of components were screened. The desired product (**8a**) was obtained in 69% yield at 70 °C for 15 min. (Table 1, entry 8). This was followed by increasing the amount of aniline (**6a**) or *tert*-butyl isocyanide (**7a**) to 1.3 equivalents, resulting in decreased yields of 65% and 66%, respectively (Table 1, entries 9, 10). In the case of changing the amount of T3P® to 2 equivalents, the yield was slightly increased to 76% (Table 1, entry 11). Reducing the amount of T3P® to 0.5 equivalents resulted in the formation of **8a** in 73% yield, but 2 h was necessary for full conversion (Table 1, entry 12). Further reducing the amount of T3P® to 0.1 equivalents gave **8a** in only 39% yield after 48 h (Table 1, entry

13). In the absence of the T3P® the product could be detected only in trace amounts by HPLC-MS (Table 1, entry 14).

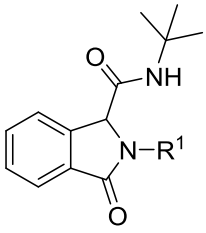
With the optimized reaction conditions in hand, the scope and limitations of the T3P®-assisted synthesis of 3-oxoisoindoline-1-carboxamides (**8**) was examined (Scheme 2). The reaction of 2-formylbenzoic acid (**5a**) with various primary aromatic amines (**6a**–**j**) and isocyanides (**7a**–**c**) was studied.

First, an isoindolinone library was synthesized using *tert*-butylisocyanide (**7a**), 1-pentylisocyanide (**7b**) or 2,6-dimethylphenylisocyanide (**7c**), and five different amines (**6a**–**e**) resulting in products **8a**–**o**. It should be noted that in the case of **7b** and **7c** the amount of T3P® could be reduced to 1.5 equivalents. Overall, the products were obtained in good to high yields (47–85%, Scheme 2).

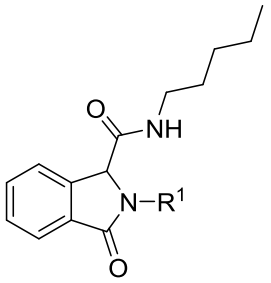
After extension of the reaction with the three isocyanides, **7c** was chosen for testing a wider scope and limitation. Using 4-methoxyaniline (**6f**) as the amine component, product (**8p**) was obtained in a reasonable yield (64%). Compound **8q** was produced in similar yield (60%) with the bulkier fluorene-2-amine (**6g**). Aryl amines containing electron withdrawing groups strongly hindered the reaction. Particularly, the use of 3,5-bistrifluoromethyl aniline (**6h**) gave product **8r** in 40% yield. Furthermore, no product formation was observed with 4-nitroaniline. Benzylamine (**6i**) showed low reactivity and the corresponding product (**8s**) was isolated in 25% yield. When the reaction was performed with 1,4-phenylenediamine (**6j**), two products were isolated, the mono- (**8t**) and the bis-isoindole derivative (**8u**) in 61% and 20% yield, respectively. Compounds **8t** and **8u** could only be separated using reverse-phase flash chromatography.



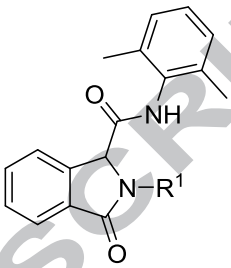
5a **6a-j** **7a-c** **8a-u**



8a R^1 = Ph, 76%

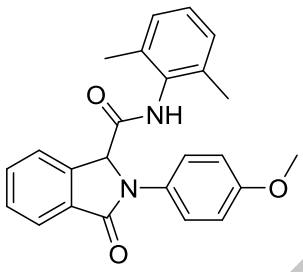


8b R^1 = Ph, 79%

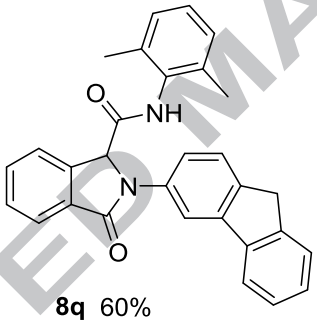


8c R^1 = Ph, 68%

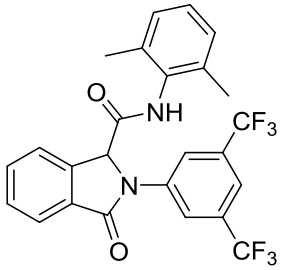
8d R^1 = 4-Me-C_6H_4, 64%
8e R^1 = 4-Me-C_6H_4, 85%
8f R^1 = 4-Me-C_6H_4, 85%
8g R^1 = 4-Br-C_6H_4, 66%
8h R^1 = 4-Br-C_6H_4, 76%
8i R^1 = 4-Br-C_6H_4, 66%
8j R^1 = 2-naphthyl, 60%
8k R^1 = 2-naphthyl, 74%
8l R^1 = 2-naphthyl, 61%
8m R^1 = 3,4,5-$(MeO)_3$-C_6H_2, 47%
8n R^1 = 3,4,5-$(MeO)_3$-C_6H_2, 70%
8o R^1 = 3,4,5-$(MeO)_3$-C_6H_2, 75%



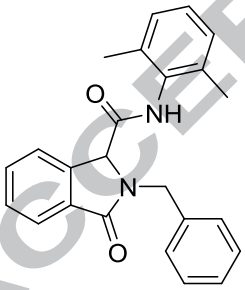
8p 64%



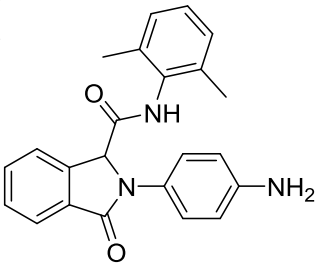
8q 60%



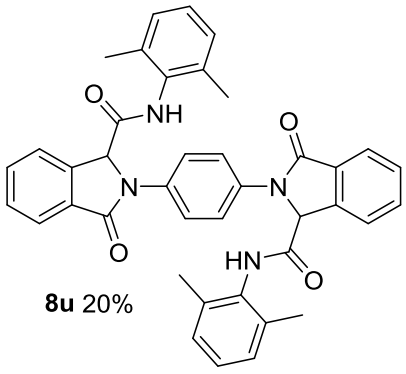
8r 40%



8s 25%



8t 61%



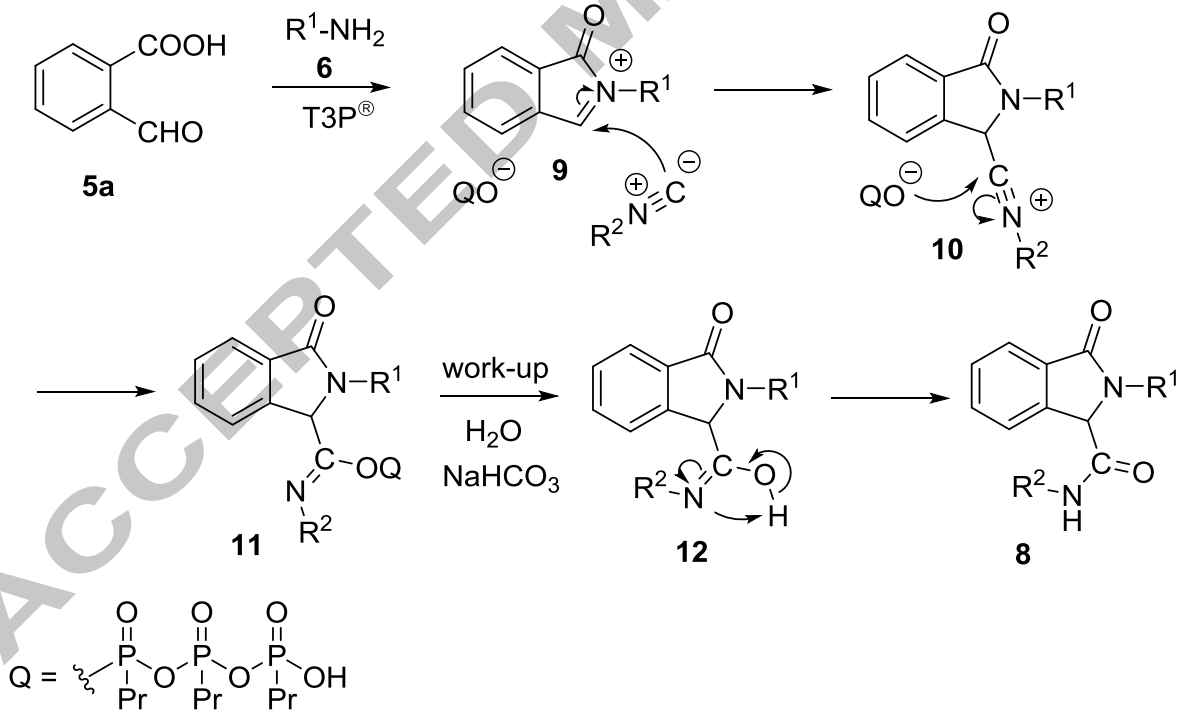
8u 20%

Scheme 2. Scope and limitations for the Ugi-4C-3CR synthesis of an isoindolinone library.

Notably, in the ^{1}H-NMR spectrum of **8s**, the two benzylic protons gave doublets at different chemical shifts (4.05 ppm and 5.34 ppm), that could be explained by their diastereotopic

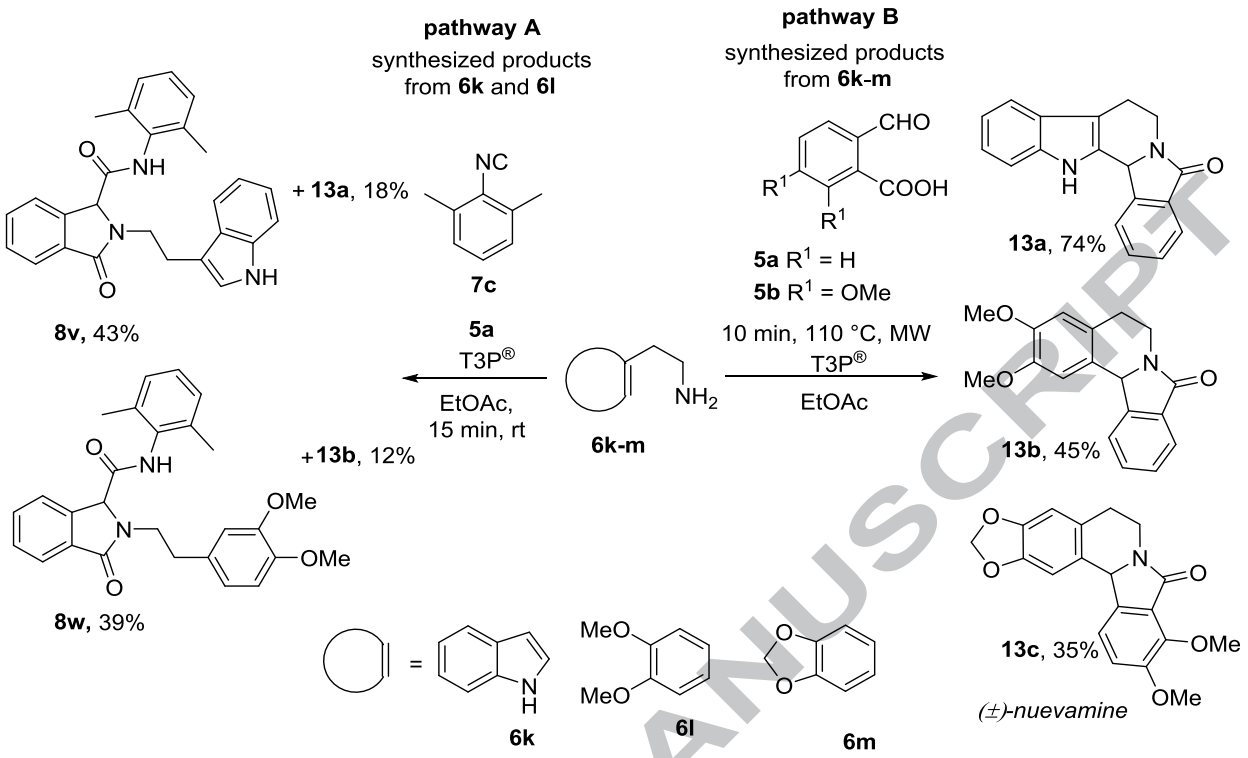
character and also by the proximity of the isoindolinone ring oxygen atom. This phenomenon was investigated with quantum chemical calculations and is presented in detail in the ESI.

A plausible mechanism for the T3P®-mediated synthesis of 3-oxoisoindoline-1-carboxamides (**8**) is outlined in Scheme 3. The reaction steps leading to heterocycle **8** presumably begins with the formation of previously reported intermediate **9**,[21] followed by addition of the isocyanide resulting in **10**. This positively charged species (**10**) is than attacked by the ring-opened anionic residue of the T3P®-water adduct (QO^-) leading to the imidic phosphonic anhydride **11**. Under aqueous work-up conditions anhydride **11** is hydrolysed resulting in the desired amide **8** after tautomerization. In order to provide evidence for this mechanism, ^1H and ^{31}P NMR measurements were performed in the presence and also in the absence of T3P®. These results support that T3P® plays a role in the scavenging of water, forming intermediate **9**, and reacting with isocyanide **10**. A detailed mechanistic study is under preparation.



Scheme 3. Proposed mechanism for the T3P®-promoted formation of isoindolinones **8**.

Next, tryptamine (**6k**) or 3,4-dimethoxyphenyl-ethylamine (**6l**) were investigated in the Ugi-4C-3CR. Besides the desired products **8v** and **8w**, formation of side-products **13a** and **13b** were also observed in 18% and 12% yield, respectively (Scheme 4, pathway A). The structure of these heterocycles was elucidated by NMR spectroscopy, and it was found that the applied isocyanide was not necessary for their formation. Thus the reaction of 2-formylbenzoic acid (**5a**) and the corresponding amine in the presence of T3P® gave compounds **13**. The reaction conditions were optimized for **13a** (Scheme 4, pathway B, Table 2). It turned out, that for the highest yield in 2 h (Table 2, entries 3–6), it was necessary to increase the amount of the amine and T3P®. The application of two equivalents of tryptamine and five equivalents of T3P® at room temperature gave product **13a** in 68% yield (Table 2, entry 5). When the reaction mixture was heated under microwave (MW) conditions,[23] the corresponding product (**13a**) was obtained in 74% yield (Table 2, entry 6). Notably, previous syntheses using sulphuric acid gave **13a** in 68% yield,[24] the application of boric acid and acetic acid gave **13a** in 96% yield,[25] and a solvent- and additive-free MW synthesis gave **13a** in 95% yield.[26] Using homoveratrylamine (**6l**) as the starting material, compound **13b** was produced in 45% yield under the same reaction conditions. Moreover, in order to utilize the above Pictet-Spengler acylation cascade, 6-formyl-2,3-dimethoxybenzoic acid (**5b**) and 2 equivalents of 2-[3,4-(methylenedioxy)phenyl]ethylamine (**6m**) were reacted under the optimized conditions, resulting in formation of the alkaloid (±)-nuevamine (**13c**) in 35% yield. This moderate yield might be explained by the decreased reactivity of the carbonyl and carboxyl groups of **5b** caused by the electron donating methoxy groups. Notably, the nuevamine skeleton has been previously synthesized from analogues of **5**, but *via* a two-step procedure.[27] To the best of our knowledge, our method represents the first one-pot synthesis of natural product (±)-nuevamine (**13c**).



Scheme 4. Reactions of compounds **5a**,**b** with tryptamine (**6k**) or phenyl-ethylamines (**6l**,**m**).

Table 2. Optimization for the reaction of 2-formylbenzoic acid (**5a**) with tryptamine (**6k**)

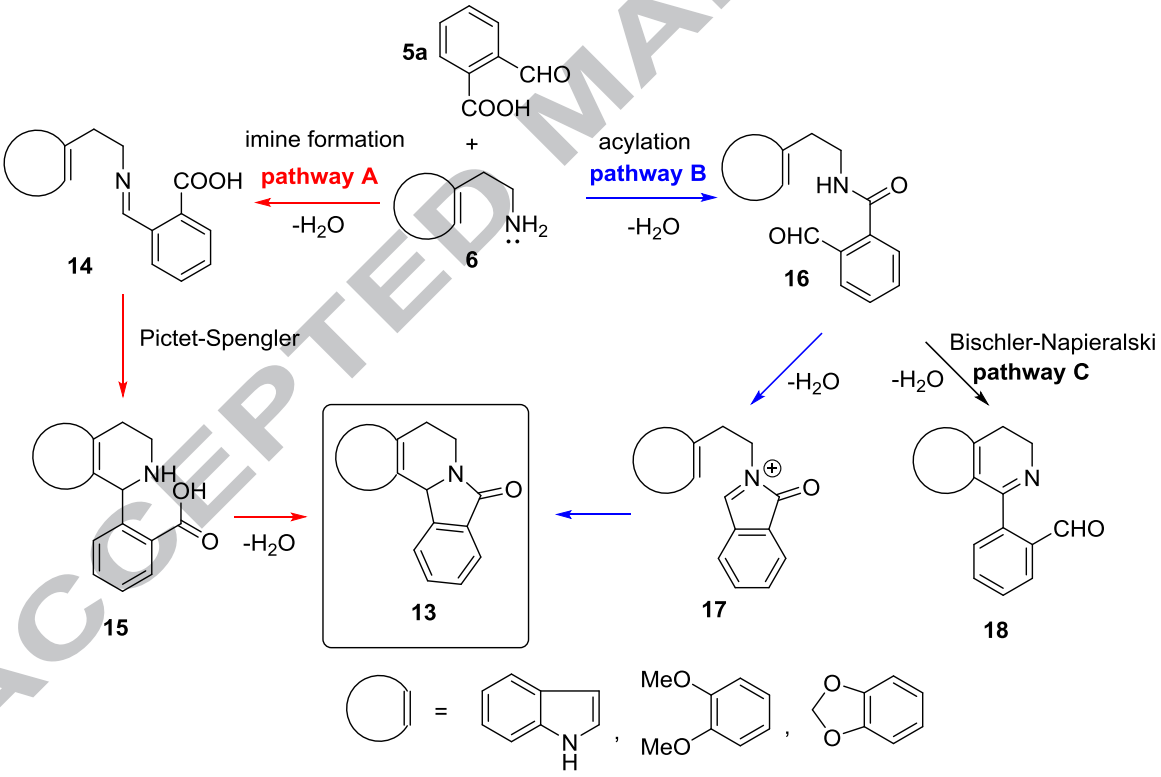
Entry	T3P® [equiv.]	6k [equiv.]	T	t	Yield 13a [%][b]
1	1.5	1	rt	24 h	23
2	3	1	rt	3 h	41
3	5	1	rt	2 h	51
4	3	2	rt	2 h	48
5	5	2	rt	2 h	68
6	5	2	110 °C[a]	10 min	74

[a]MW irradiation.

[b]Isolated yield

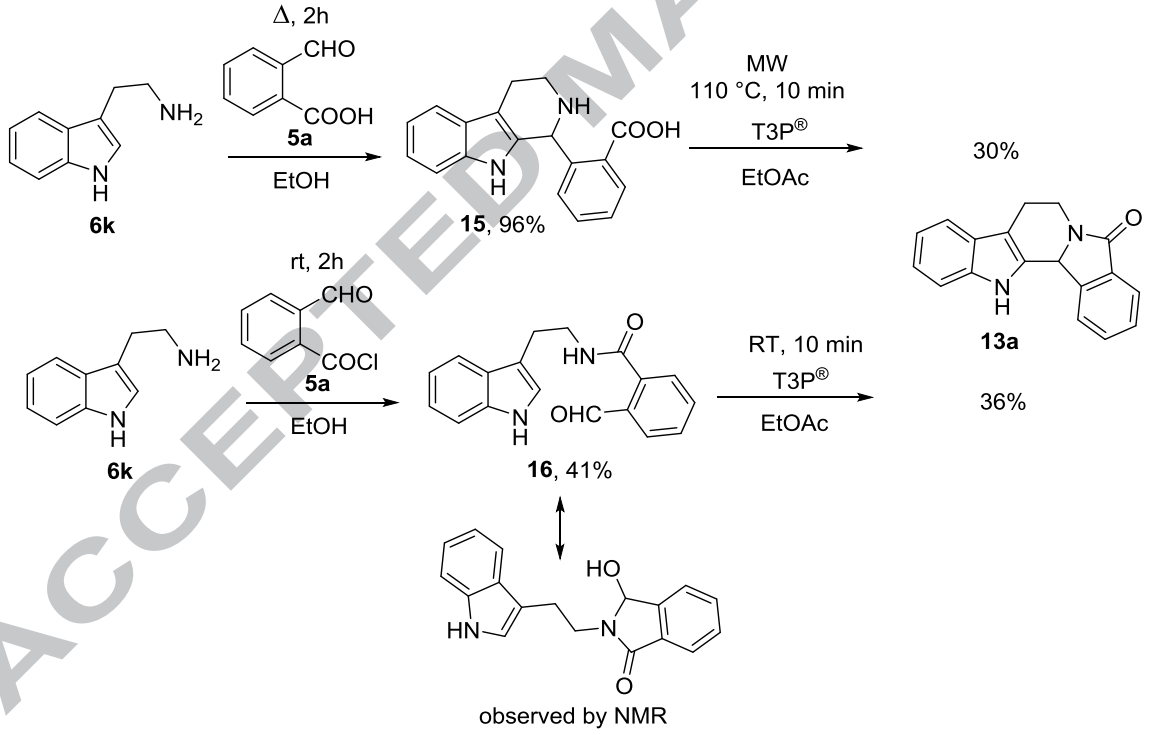
The mechanism for the formation of compounds **13** could be envisaged two ways (Scheme 5). In the first case, the primary amine (**6**) and 2-formylbenzoic acid (**5a**) presumably forms imine **14** and the heterocyclic ring is closed *via* a Pictet-Spengler cyclization leading to carboxylic acid **15** (Scheme 5, pathway **A**, red arrows). This might be followed by

intramolecular acylation resulting in heterocycle **13**. In the second case, acylation of the amine (**6**) by 2-formylbenzoic acid (**5a**) and subsequent reaction of the aldehyde functional group with the amidic NH (**16**) might form an iminium intermediate (**17**) that leads to **13** through a Pictet-Spengler ring closure (Scheme 5, pathway **B**, blue arrows). However, in parallel with this pathway, the Bischler-Napieralski ring closure of **16** cannot be excluded, which is also supported by the observation that 6,7-dimethoxy-1-(2-formylphenyl)-3,4-dihydroisoquinoline (**18**) was detected by HPLC-MS and its structure was determined by ^{1}HNMR in the crude reaction mixture (Scheme 5, pathway **C**, black arrow). Moreover, when monitoring the reactions of **5a** with **6k** and **6l**, imine **14** could be distinguished by HPLC-MS from amide **16**, which was formed only in 20% and 6%, respectively, supporting the dominance of pathway A.



Scheme 5. Proposed T3P®-mediated reaction mechanisms for the formation of heterocycles **13**.

In order to provide evidence for the above mechanisms, additional experiments were performed (Scheme 6). Imine **14** could not be isolated from the reaction of **5a** and **6k** without any additive or in the presence of $MgSO_4$ or T3P®, which can be explained by its low stability.[28] However, in the reaction of **5a** and **6k** in ethanol at reflux,[29] 2'-carboxyphenyl-1,2,3,4-tetrahydro-β-carboline (**15**) was isolated in 96% yield. When **15** was reacted in the presence of 5 equivalents of T3P® under MW conditions at 110 °C for 10 min, the desired product **13a** was formed in 30% yield. Considering pathway B, firstly, amide **16** was synthesized *via* the acylation of tryptamine with 2-formylbenzoyl chloride. Notably, in the ^{1}H and APT NMR spectra the cyclized 3-hydroxyisoindolinone was observed as the stable isomer. It was also observed that the reaction proceeded in solution already at room temperature without any additive. Adding 5 equivalents of T3P® over 10 min resulted in full conversion, the HPLC chromatogram showed **13a** and **18** in a 13:1 ratio. Heterocycle **13a** was isolated in 36% yield.



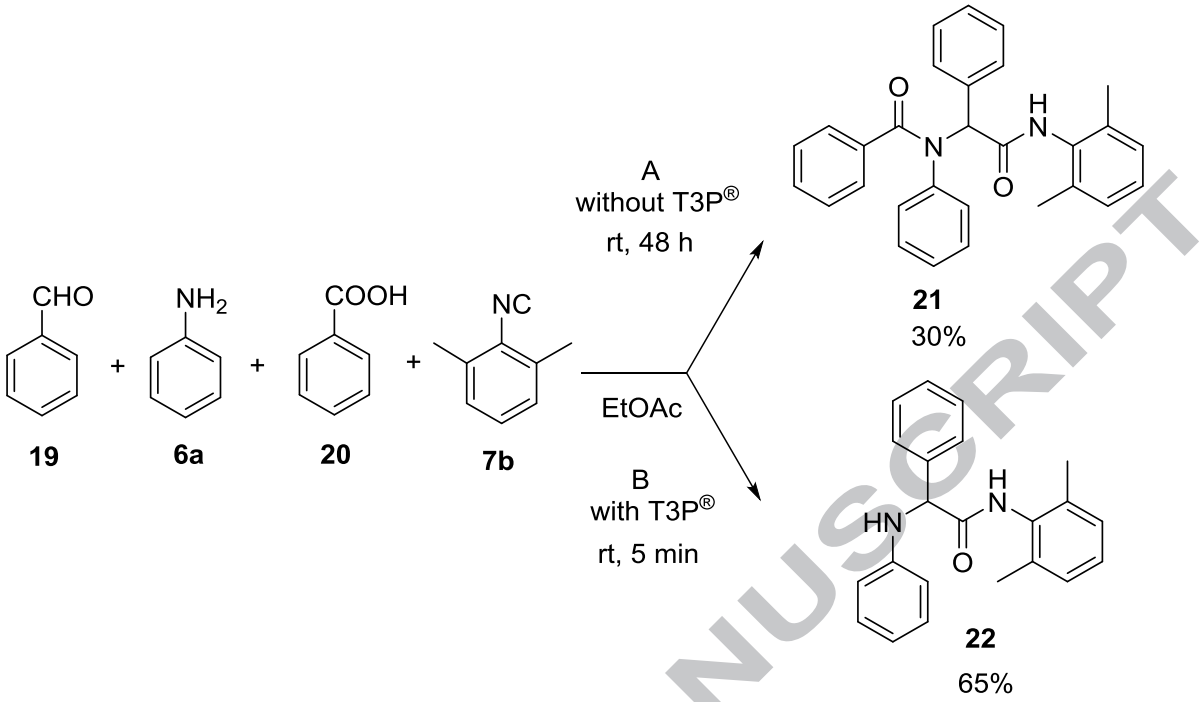
Scheme 6. Reactions supporting the proposed reaction mechanisms.

Based on this preliminary experimental investigation of the proposed mechanistic pathways one can see the dominance of pathway A starting with imine formation following by Pictet-

Spengler cyclization. Nevertheless, pathway B is also conceivable, but in a much smaller amount.

Finally, attempts were made to extend the reaction to 2-acetylbenzoic acid. However, in this case we could not obtain the desired product, and only the formation of 2-formylbenzanilide was observed by HPLC-MS, which might be explained by the decreased reactivity of the electron rich acetyl oxo group than that of the formyl derivative.

Following the heterocycle synthesis, we were motivated to investigate the role of T3P® in a traditional Ugi-4CR of benzaldehyde (**19**), aniline (**6a**), benzoic acid (**20**), and 2,5-dimethylphenyl isocyanide (**7c**). Reacting these four components in ethyl acetate gave the desired α-aminoacyl amide (**21**) in 30% yield after 48 h (Scheme 7, pathway A). In the presence of T3P® the formation of **21** was not observed, but instead, β-aminoamide **22** was isolated in 65% yield after 5 min (Scheme 7, pathway B).[22] The reaction was monitored by TLC and HPLC-MS and the conversion did not increase even after 24 h. From this result it could be concluded that T3P® promotes formation of the imine from aniline **6a** and benzaldehyde **19**, but hinders the role of the carboxylic acid in the Ugi-reaction protonating the imine intermediate before attack of the isocyanide.[22]



Scheme 7. Investigation of the classical Ugi-4CR

Conclusion

A novel T3P®-promoted synthetic procedure was developed for the synthesis of isoindolinones (**8**) in a one-pot, multicomponent Ugi-reaction from 2-formylbenzoic acid (**5a**). The scope and limitations of the reaction was demonstrated by the application of various amines (**6**) and isocyanides (**7**). A side reaction was observed in the reaction of tryptamine (**6k**) and phenylethylamine derivatives (**6l**,**m**) that was optimized and applied for the first one-pot synthesis of the alkaloid (±)-nuevamine (**13c**). Proposals have been presented for possible reaction mechanisms supported by additional experiments. Finally, it was observed that the Ugi-4CR was not successful in the presence of T3P®.

Acknowledgement

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Highlights

- T3P® was applied successfully in an Ugi four-center three-component reaction
- An isoindolinone library was synthesized in a short reaction time with good yields
- The scope and limitations was shown applying of various amines and isonitriles
- A side reaction was extended for the synthesis of the alkaloid *(±)-nuevamine*

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