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Decarboxylative coupling reaction of 2-(1*H*-indol-3-yl)acetic acids with indole, azaindole, benzimidazole and indazole derivatives

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Abstract. 3,3'-Diindolylmethanes (DIMs) are an important class of indole alkaloids that exhibit anti-inflammatory and anti-cancer effects. Herein, we report on a new, mild and efficient copper(II)-promoted decarboxylative coupling reaction of 2-(1*H*-indol-3-yl)acetic acid derivatives (**1a-h**) with a variety of (substituted) indoles (**2a-t**) yielding (un)symmetrically substituted DIMs (**3a-z**, **3aa-ai**). Reaction of 2-(1*H*-indol-3-yl)acetic acid (**1a**) with 7-azaindole led to the 3,3'-connected DIM analog **5d** while 4-, 5-, and 6-azaindoles and benzimidazole reacted at the *N*1-nitrogen atom. Reaction of **1a** with 1*H*-indazoles led to a mixture of 1- and 2-substituted indazole derivatives. The new method allows large-scale synthesis of biologically active DIMs.

Keywords: C-C bond formation; decarboxylative coupling; diindolylmethanes; unsymmetrical diindolylmethanes; large-scale synthesis

Introduction

Diindolylmethanes (DIMs) are an important class of indole alkaloids that consist of two indole rings connected by a methylene unit. Unsubstituted DIM, a major bioactive metabolite of glucobrassicin found in cruciferous vegetables, is clinically evaluated for the treatment of prostate cancer,[1] and there is preclinical evidence for its activity against other types of cancer as well.[2,3,4] Several recent studies reported on various biological targets for DIM including the arylhydrocarbon receptor,[5-7] the immunostimulatory G protein-coupled receptor 84 (GPR84),[8] the histone deacetylase-1 (HDAC-1)[9] and the cannabinoid receptor 2 (CB_2).[10]

To optimize the potency of DIM derivatives for specific targets with the aim to develop a drug, synthetic procedures are required that allow broad modification of the scaffold. Most of the described synthetic methods for DIM derivatives only yield symmetrical products.[11] However, binding sites of protein targets are typically unsymmetrical in nature.

Recently, we reported on a general and efficient synthetic approach towards unsymmetrical DIMs by reaction of (3-indolylmethyl)trimethylammonium iodides with substituted indole derivatives.[12] Although the reaction is efficient, (3-indolylmethyl)trimethylammonium iodides have to be prepared as starting compounds requiring an additional step, and the formation of trimethylamine as a by-product reduces the atom economy. Therefore, we decided to search for new alternative methodologies to prepare (un)symmetrical DIMs.

Recently, decarboxylative coupling reactions of carboxylic acids have become of primary importance for C-C and C-X (X = N, P, S) bond formation.[13] Carboxylic acids are commercially available or easily accessible, non-toxic, and highly stable, and therefore represent ideal starting materials.[14] Decarboxylative coupling reactions are simple to operate and generally do not produce toxic by-products. We have now developed an efficient Cu(II)-promoted decarboxylative coupling reaction of indole-2-(1*H* indol-3-yl)acetic acid derivatives for the preparation of 3,3'-diindolylmethanes, which provides a straightforward access to a wide range of (un)symmetrical 3,3'-DIMs. The developed procedure has a broad substrate scope with excellent functional group tolerance, it proceeds with high regioselectivity

and atom economy. Moreover, it represents the first reported procedure for the preparation of (aza)DIM derivatives by a decarboxylative coupling reaction, which can be utilized for the synthesis of unsymmetrical as well as symmetrical DIM derivatives.

Results and Discussion

The decarboxylation coupling reaction of 2-(1*H*-indol-3-yl)acetic acid (**1a**) with 5-methoxyindole (**2a**) was initially investigated as a model reaction (see Table 1). No product was formed when the reaction was carried out without the presence of catalyst and oxidant (entry 1). Next, different oxidants and catalysts were screened. A mixture of $Cu(OAc)_2 \cdot H_2O$ (1 equiv.) as an oxidant with 10 mol% Ag_2CO_3 as a catalyst in acetonitrile at 115 °C for 8 h (entry 2, 55% yield) exhibited higher reactivity than the addition of $Pd(OAc)_2$ as a catalyst (entry 3, 37% yield). Various oxidants including Ag_2CO_3, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), $Na_2S_2O_8$, *tert*-butyl peroxide, benzoquinone, H_2O_2, $PhI(OAc)_2$, or O_2 in the presence of 10 mol% $Cu(OAc)_2 \cdot H_2O$, did not improve the yield (entry 3-11, 15-39 %) or resulted only in trace amounts of product (entry 5, 7). As a next step, the reaction was performed only in the presence of catalyst. With $Pd(OAc)_2$ as a catalyst, no product was formed (entry 12), while $Cu(OAc)_2 \cdot H_2O$ or Ag_2CO_3 led to 39% or 30% product formation (entry 13, 14), respectively. Interestingly, when Ag_2CO_3 (entry 15) or $Cu(OAc)_2 \cdot H_2O$ (entry 16) were used as oxidants in the reaction, the formation of product was increased to 45% or 60%. When the amount of the oxidant $Cu(OAc)_2 \cdot H_2O$ was increased from 0.57 mmol to 1.14 mmol, no significant change was observed (62% yield, entry 17). These observations imply that $Cu(OAc)_2 \cdot H_2O$ alone as an oxidant without any catalyst is effective for the decarboxylative coupling reaction.

The screening of oxidants including CuO (entry 18, yield 52%), Cu(0) (entry 19, yield 53%), CuF_2 (entry 20, yield 51%), $CuCl_2$ (entry 21, no reaction), $AuCl_2$ (entry 22, no reaction) and $CuSO_4 \cdot 5H_2O$ (entry 23, yield 41%) did not improve the yield as compared to $Cu(OAc)_2 \cdot H_2O$ or did not result in product formation at all (entry 21 and 22). This result suggests that $Cu(OAc)_2 \cdot H_2O$ is superior to other oxidants.

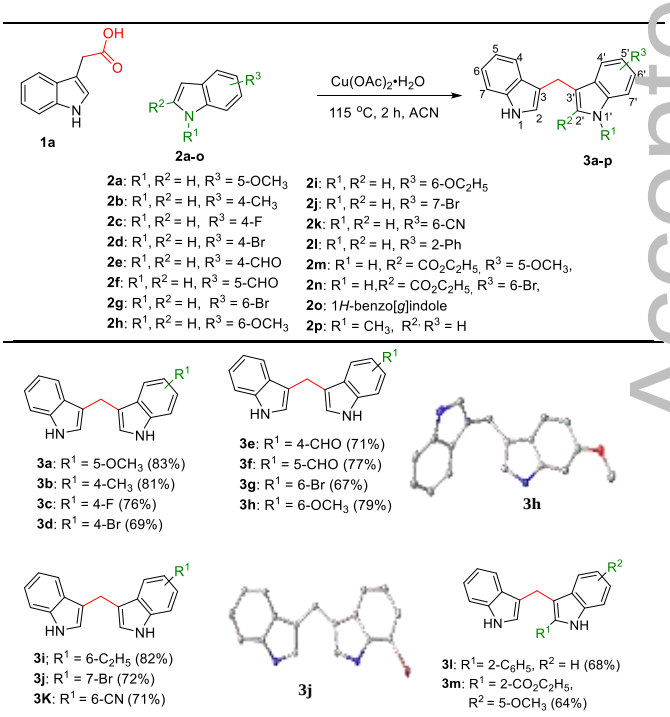
We next investigated the ratio of the reagents indolylacetic acid **1a** and indole **2a**. At first, we increased the amount of **1a** from 0.57 mmol to 1.14 mmol and reacted it with **2a** (0.57 mmol). This led to an acceleration of the reaction, which was completed within 2 h as compared to 8 h with equimolar amounts of the reaction partners; however, the formation of the desired product was reduced from 60 to 40% (entry 24). When, reversely, the amount of **2a** was increased from 0.57 mmol to 1.14 mmol, the yield of the product was increased to 83% (entry 25) within a reaction time of 2 h. Increasing the amount of **2a** to 1.71 mmol (3 equiv.) did not lead to further increase in the yield (80%, entry 26).

Next, we investigated how temperature affected the reaction (see Table S1). Upon increasing the temperature from 115 to 125 °C, the yield of the product was slightly reduced to 74% (entry 1). Reducing the temperature from 115 °C to 100, 90 or 80 °C reduced the yield (entries 2-4) or resulted in no reaction (entry 24).

As a next step, the effect of solvent was investigated (see Table S1). Solvents such as DMF (entry 6, yield 60%), ethanol (entry 7, yield 35%), chlorobenzene (entry 10, yield 20%), DMSO (entry 11, yield 57%), or H_2O (entry 13, yield 30%) did not improve the yield as compared to acetonitrile. In dichloromethane (entry 8), dichloroethane (entry 9), and tetrahydrofuran (entry 12), no reaction was observed.

With the optimized conditions ($Cu(OAc)_2 \cdot H_2O$, 115 °C for 2 h in ACN, Table 1, entry 25), we investigated the scope of the reaction employing various indole derivatives, which were reacted with carboxylic acid **1a** to prepare unsymmetrical DIMs (**3a-p**, Table 2). In general, the reactions of **1a** with differently substituted indoles proceeded well and yielded the desired products in good to excellent yields (55-83%).

Table 2. Exploration of the scope of the reaction employing various indoles[a-d]



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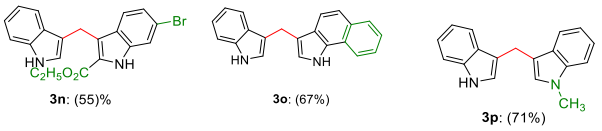
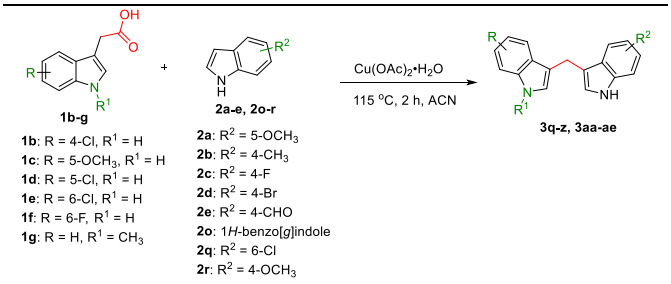
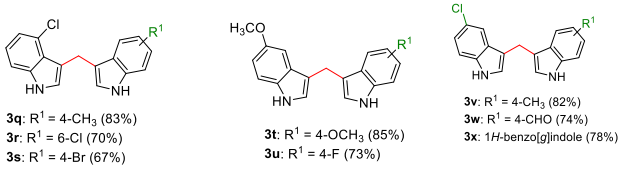


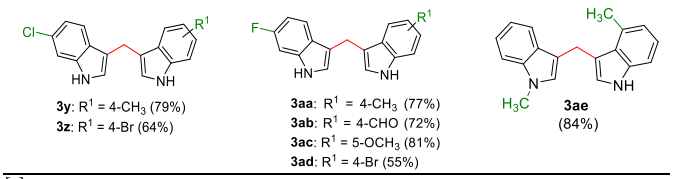
[a] All reaction was carried out an a 0.57 mmol (**1a**) in 5 mL of solvent in presence of 1 eq. $Cu(OAc)_2 \cdot H_2O$ at 115 °C for 2h; [b]All isolated products were characterized by ^1H and ^{13}C NMR spectra. For **3h** and **3j** X-ray crystal structures were additionally obtained.[15] In addition, HPLC analysis coupled to electrospray ionization mass spectrometry (LC-ESI-MS) was performed; [c]Isolated yields; [d]Purity was determined by HPLC coupled to a UV diode array detector (DAD) at 220-400 nm.

Both electron-donating and electron-withdrawing groups were tolerated. Electron-donating substituents as in 5-methoxyindole (**2a**), 4-methylindole (**2b**), 6-methoxyindole (**2h**), 6-ethoxyindole (**2i**) resulted in excellent yields (**3a-b**, **3h-i**: 79-83%). Compound **3a** had previously been reported to be a potent agonist of the immunostimulatory receptor GPR84.[8] The coupling of indoles substituted with electron-withdrawing groups such as 4-fluoroindole (**2c**), bromoindoles (**2d**, **2g**, **2j**), indole-4-/5 carboxaldehydes (**2e**/**2f**) and 6-cyanoindole (**2k**) with carboxylic acid **1a** delivered the desired products in good to excellent yields (**3c-g**, **3j**, **3k**: 67-77%). Indoles substituted with carboxylic acid esters or phenyl groups at position 2 (**2l**, **2m** and **2n**) yielded the desired products **3l-n**, in somewhat lower yields (55-68%) probably due to steric hindrance. Reaction of **1a** with the tricyclic 1*H*-benzo[*g*]indole (**2o**) or *N*-protected indole **2p** provided **3o** (67%) or **3p** (71%) in good yields.

Table 3. Reactions of differently substituted 2-(1*H*-indol-3-yl)acetic acid derivatives with substituted indoles[a,b]







[a] All reaction was carried out an a 0.57 mmol (**1b-g**) in 5 mL of solvent in presence of 1 eq. $Cu(OAc)_2 \cdot H_2O$ at 115 °C for 2h; [b] isolated yield.

Next, we investigated a variety of substituted indole-3-acetic acid derivatives (**1b-g**) for the preparation of DIMs (**3p-z**, **3aa-ae**). Different functional groups, including Cl, OMe, and F in different positions of the indole ring were tolerated, and the desired products were generally obtained in good to excellent yields (59-85%).

It was noticed that electron-withdrawing substituents such as Cl or F on the phenyl ring of indoleacetic acid (**1b**, **1d**, **1e**, **1f**) led to more efficient reactions as compared with indole derivatives bearing electron-donating groups (**2a**, **2b**) providing the desired products in excellent yields ranging from 77-83%. On the other hand, the coupling reaction of indoleacetic acids substituted with electron-withdrawing groups such as Cl or F (**1b**, **1d**, **1e**, **1f**) with indole derivatives bearing electron-withdrawing groups, including F (**2c**), Br (**2d**), CHO (**2e**), or Cl (**2q**), led to the desired products but in lower, still in good yields (**3r-s**, **3w**, **3z**, **3ab**, **3ad**: 59-74%). Reaction of 5-methoxyindoleacetic acid (**1c**) with 4-methoxyindole (**2r**), or 4-fluoroindole (**2c**), respectively, delivered the corresponding products in excellent yields (**3t**: 85%, **3u**: 73%). Moreover, the coupling of *N*1-methyl-3-indoleacetic acid (**1g**) with 4-methylindole (**2b**) proceeded well yielding 84% of product **3ae**. In addition, the reaction of 5-chloroindoleacetic acid with 1*H*-benzo[*g*]indole provided the product **3x** (78%) in very good yield.

Next, we investigated this protocol for preparing (un)symmetrical DIMs at a larger scale as required for biological studies. We performed gram scale reactions of indole-3-acetic acid (**1a**, 5.7 mmol) with 5-fluoroindole (**2s**, 11.4 mmol), of 5-methoxy-3-indoleacetic acid (**1c**, 4.8 mmol) with 5-methoxyindole (**1a**, 9.7 mmol), and of 5-fluoro-3-indoleacetic acid (**1h**, 5.2 mmol), with 5-fluoroindole (**2s**, 10.4 mmol) (Scheme 1). In all reactions, we obtained the desired products in very good yields (**3af**: 72%, **3ag**: 83% and **3ah:** 76%). Compounds **3af-ah** had previously been reported as potent agonists of the immunostimulatory receptor GPR84 and these compounds are of importance as pharmacological tools.[8]

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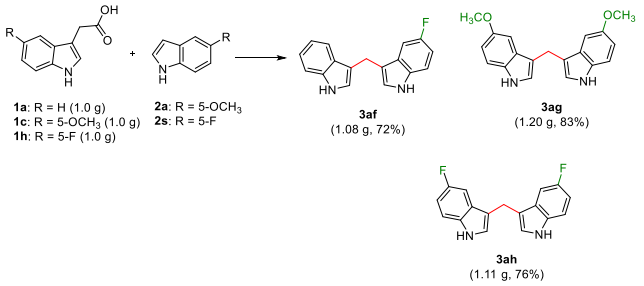
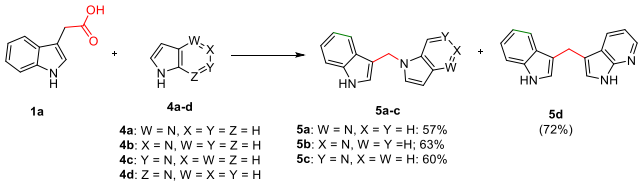


Scheme 1. Gram-scale synthesis of (un)symmetrical DIMs **3af-ah**, which are potent agonists of the orphan G protein-coupled receptor GPR84.

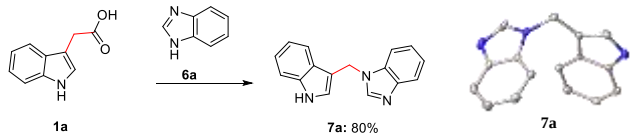
It is worth noting that the reactions are highly regioselective as the decarboxylative alkylation occurs exclusively in the 3-position of indoles as confirmed by ^{1}H, and ^{13}C NMR spectroscopy. Additionally, X-ray analysis of representative examples, including **3h** and **3j**, unambiguously confirmed that the coupling reaction had occurred at the 3-position of the indole ring. Many functional groups including chloro and bromo substituents as well as carboxaldehyde and carboxylic acid ester groups remained intact, providing opportunities for further derivatization.

Next, the protocol was applied to prepare azaindole derivatives. We observed that the coupling reaction of **1a** with 4-, 5- or 6-azaindole (**4a-c**), yielded the *N*1-alkylated products (**5a-c**, Scheme 2), whereas reaction with 7-azaindole (**4d**) afforded the 3,3'-coupled product **5d** in good yields. Compound **5d** was previously reported to possess anticancer activity.[16]



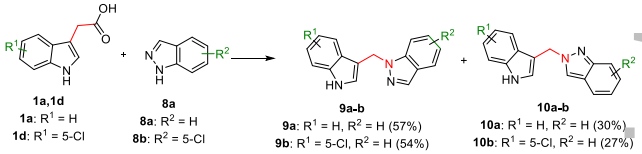
Scheme 2. Decarboxylative coupling reaction of **1a** with azaindoles **4a-d**.

The coupling reaction of **1a** with 1*H*-benzimidazole (**6a**) afforded **7a** in an excellent yield of 80% (Scheme 3). The structure of the product was confirmed by X-ray crystallography.[15] Compound **7a** was previously reported to possess anti-fungal and anti-convulsant activities.[17]



Scheme 3. Decarboxylative coupling of **1a** with 1*H*-benzimidazole (**6a**).

We further studied the coupling reaction of indole-3-acetic acid derivatives with 1*H*-indazoles. As depicted in Scheme 4, the reaction of **1a** or **1d** with 1*H*-indazoles **8a-b** yielded mixtures of *N*1- (**9a**: 57%, **9b**: 54%) and *N*2-subsitututed indazoles (**10a**: 30%, **10b**: 27%). We observed that the *N*1-substituted products were obtained in higher yields as they are thermodynamically favoured; the combined overall yields of **9** and **10** were excellent. Compound **9a** had previously been prepared by reaction of 3-hydroxymethylindole with 1*H*-indazole in the presence of metallic sodium at 100 °C for 9 h. However, the yield of **9a** obtained in that reaction was significantly lower (13.8%) when compared to the present method (57%).[16]

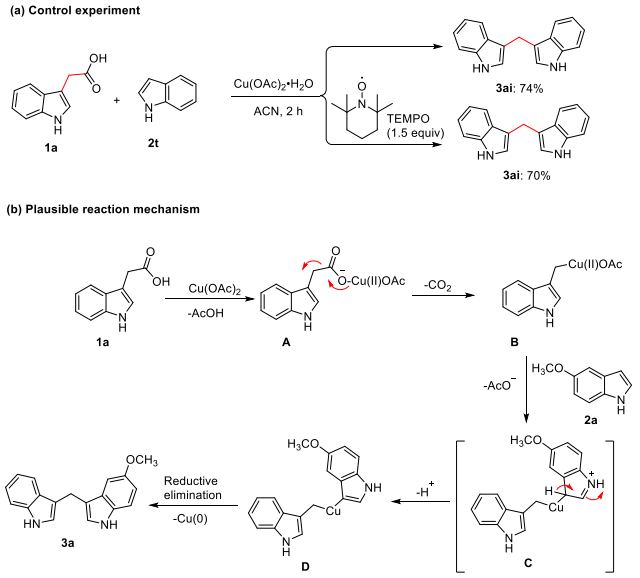


Scheme 4. Decarboxylative coupling reaction of **1a** and **1d** with 1*H*-indazole derivatives (**8a-b**).

Finally, we applied the developed protocol to reactions of 2-(1-benzofuran-3-yl)acetic acid, and benzo[*b*]thiophene-3-acetic acid, respectively, with 5-methoxyindole (**2a**). However, no desired products were formed although many spots appeared on TLC. These results suggest that the presence of the *N*-atom is important for reactivity, which may stabilize the indolinium-copper(II) complex (*e.g.* see intermediate B in Scheme 5) through 1,3-conjugation during the reaction. We also studied the reaction of 3-indolepropionic acid with 5-methoxyindole (**2a**) under the same reaction conditions, but no reaction took place. In a further attempt, we performed the reaction of indole-3-glyoxalic acid with **2a** under decarboxylative coupling conditions, but the desired product was not obtained. These observations suggest that upon decarboxylation, the formation of a benzylic type intermediate complex with Cu(II) is important for reactivity (*e.g.* see intermediate B in Scheme 5), which cannot be formed in case of the reaction of 3-indolepropionic acid and indole-3-glyoxalic acid.

Although the exact mechanism of the decarboxylative coupling reaction is not completely clear, a plausible mechanism is proposed for the synthesis of **3a** in Scheme 5. In order to understand if this reaction was mediated *via* a radical mechanism, we performed control experiments in the presence of 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO). As depicted in Scheme 5a, reaction of indole-3-acetic acid (**1a**) and indole (**2t**) was carried out in the absence or in the presence of TEMPO. Under both conditions, the product DIM (**3ai**) was produced in excellent yields (74% and 70%) suggesting that radicals did not play a role in this reaction. Based on literature,[17] indole-3-acetic acid (**1a**) reacts with $Cu(OAc)_2$ affording a Cu(II) carboxylate species (A). Elimination of CO_2 (B) followed by nucleophilic substitution of 5-

methoxyindole (**2a**) affords intermediate C. Re-aromatization of C *via* C-H bond cleavage generates D, which then undergoes reductive elimination to produce the desired coupling product **3a** along with elemental copper.



Scheme 5. (a) Control experiment and (b) proposed reaction mechanism for DIM derivative **3a** as an example.

Conclusion

In conclusion, we developed an efficient copper(II)-promoted decarboxylative coupling reaction of indole-2-(1*H*-indol-3-yl)acetic acids and indoles for the preparation of (un)symmetrical 3,3'-DIMs, which are of significant interest due to their biological activities, especially in inflammation, immunity and cancer. The developed new synthetic method for (un)symmetrical 3,3'-DIMs employs mild reaction conditions, is operationally simple, and provides these valuable products in high yields. The reaction has a broad substrate scope with good functional groups tolerance and proceeds with high regioselectivity. Reactions of indole-2-(1*H*-indol-3-yl)acetic acids with azaindoles produced different *N*-substituted products depending on the position of the *N*-atom in the ring, which governs the electron densities in the ring system. The target molecules obtained in gram scale will allow comprehensive biological studies.

Experimental Section

General procedures for the synthesis of 3a-z, 3aa-ai, 5a-d, 7a, 9a-b, 10a-b. To the solution of 2-(1*H*-indol-3-yl)acetic acids (**1a-h**, 0.57 mmol) in ACN (5 mL) in a 50 mL sealed tube, indole derivatives, azaindoles, benzimidazoles, or indazoles (1.14 mmol) and $Cu(OAc)_2 \cdot H_2O$ (0.57 mmol) was charged. The reaction mixture was stirred at 115 °C for 2 h. After completion of the reaction (monitored by TLC), the mixture was cooled to room temperature. Reaction mixture was poured into water and extracted with ethyl acetate (2 X 25 mL). The combined organic layers were washed with brine solution (25 mL), dried over Na_2SO_4, and evaporated under reduced pressure to the dryness. The crude product was purified by either recrystallization or column chromatography.

Acknowledgements

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FULL PAPER

Decarboxylative coupling reaction of 2-(1*H*-indol-3-yl)acetic acids with indole, azaindole, benzimidazole and indazole derivatives

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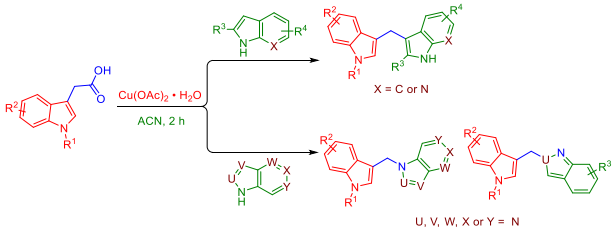

[Practical & mild conditions] [Broad scope, good functional group tolerance, high regioselectivity & atom economy] [55-85% yield, gram scale synthesis possible] [44 examples, 29 new compounds]