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Letter

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Copper-Catalyzed Synthesis of Indoles and Related Heterocycles in Renewable Solvents

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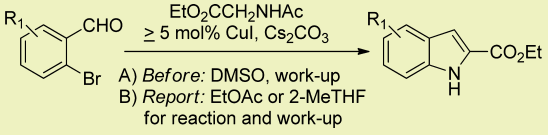
Supporting Information

ABSTRACT: An efficient one-pot cascade to indoles and related fused heterocycles has been demonstrated in renewable solvents, thereby eliminating the previously required dipolar aprotic solvent. The copper-catalyzed reaction proceeds with a range of bromobenzaldehydes to give products in good yields. In addition, the external ligand-free cross-coupling methodology provides convenient access to an investigational treatment for central nervous system disorders.



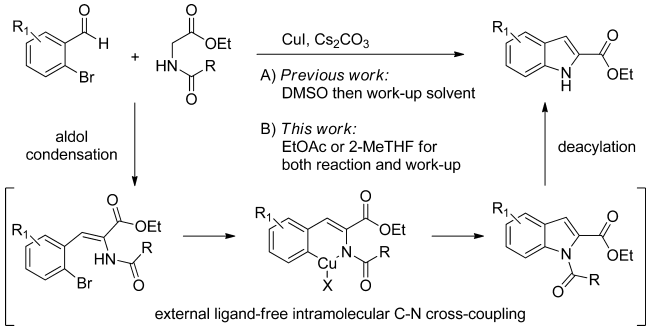
KEYWORDS: *Sustainability, Green chemistry, Renewable, Pharmaceutical, Dipolar aprotic solvent, One-pot, Cascade, Indole, Heterocycle, Catalysis*

INTRODUCTION

The indole nucleus is recognized as one the foremost biologically significant moieties in nature and has delivered several pharmaceutically intriguing compounds.[1−8] Accordingly, it has been the target of numerous synthetic strategies.[9−24] Other fused heterocycles—notably furopyrroles—have shown promise in the treatment of central nervous system (CNS) disorders, including schizophrenia, pain, and neurodegeneration.[25−32] Often, the synthetic methods applicable to the indole ring system can also be utilized for these related fused heterocycles.[33−37] Unfortunately, many of the strategies to indoles and other heterocyclic structures make use of undesirable reagents, conditions, and/or solvents.

With a well-recognized need to reduce the environmental footprint of pharmaceutical processes, new—and greener—technologies are a current industry focus.[38] We previously reported a catalytic method to access diverse indole-2-carboxylic esters under mild conditions in the absence of an external ligand.[24] This atom-economical[39] and copper-catalyzed methodology proceeded via a presumed three-step sequence—(1) aldol condensation, (2) intramolecular C−N cross-coupling via an advantageous six-membered cupracycle (X = I or Br) in a Goldberg-type reaction,[40,41] and (3) deacylation (Scheme 1)—to give the key heterocycles in good yields. Yet the reaction utilized dipolar aprotic solvents, media that negate any environmental benefit gained in reaction solubility by requiring large amounts of additional organic solvent and water to recover the product during workup.[42,43] Typically, dipolar aprotic media are also not easily substituted, a contemporary topic of discussion in green chemistry circles.[44−49] Herein, we report that the simple and efficient one-pot three-step transformation can be conducted in more benign solvents available from renewable resources.

Scheme 1. Greener Formation of Indoles and Related Heterocycles



RESULTS AND DISCUSSION

In our earlier report, we showed that iodo- (X = I) or bromobenzaldehydes (X = Br) and glycine amido esters were coupled in dimethyl sulfoxide (DMSO) under moderate temperatures to efficiently give indole-2-carboxylic esters (Table 1). This transformation was possible both in the presence and absence of diamine ligand. The corresponding chlorides (X = Cl) were not cooperative with the mild conditions, regardless of whether the ligand was included. While pleased with the success of the iodo-substituted substrates, we proceeded to investigate the scope of the ligandless reaction with ethyl acetamidoacetate (R_2 = Me) and the bromo-substituted variants (X = Br) due to greater commercial availability as well as a focus on prevention of toxic byproduct iodide salt waste.[50,51]

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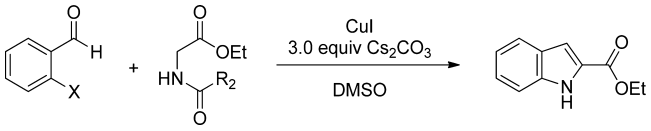
Table 1. Initial Investigation of One-Pot Three-Step Formation of Ethyl 1*H*-Indole-2-carboxylate



entry	X	R_2	mol % Cu	mol % L	*T* (°C)	yield (%)[a]
1[b]	I	Ph	20	25	60	74
2[b]	Br	Ph	20	25	60	55
3[b]	Cl	Ph	20	25	60	ND
4	I	Me	10	--	25	61
5	Br	Me	20	--	25	47
6	Br	Me	20	--	80	53
7[c]	Cl	Me	20	--	140	16

[a]Isolated yields (4.0 mmol 2-halobenzaldehyde, 1.2 equiv $EtO_2CCH_2NHCOR_2$, 16 h). [b]Reactions with *N*,*N*′-dimethylethylenediamine ligand (L = DMEDA). [c]No conversion observed at 80 °C; severe decomposition at 140 °C.

Following a catalyst and solvent screen (Table 2), we found that (1) copper(I) iodide was the superior mediator for the ligandless reaction in DMSO (entries 1−3) and (2) most organic solvents failed to give good conversion (compare entries 4−10). This was unsurprising, as dipolar aprotic solvents—DMSO, DMF, etc.—are believed to best compensate for the absent external ligand in C−N cross-couplings.[52] However, we eventually uncovered a select few media with lower dipoles and reduced dielectric strengths (entries 11 and 12) that also allowed the desired reaction to occur. 2-Methyltetrahydrofuran (2-MeTHF) and ethyl acetate (EtOAc), both solvents available from sustainable resources,[53,54] gave ethyl 1*H*-indole-2-carboxylate in comparable yields to DMSO.[55,56] In addition, these media obviated the need for gratuitous organic solvent and excess water in the aqueous workup due to sufficient phase separation and no need to remove the DMSO reaction solvent.

Table 2. Examination of Copper Catalyst and Solvent

entry	catalyst	solvent	yield (%)[a]
1	CuI	DMSO	50
2	CuBr	DMSO	33
3	CuCl	DMSO	31
4	CuI	CH_3CN	36
5	CuI	DMF	45
6	CuI	NMP	12
7	CuI	EtOH	5
8	CuI	MEK	ND
9	CuI	toluene	21
10	CuI	dioxane	19
11	CuI	2-MeTHF	59
12	CuI	EtOAc	54

[a]Isolated yields (4.0 mmol 2-bromobenzaldehyde, 1.2 equiv EtO_2CCH_2NHAc, 20 mol % CuI, 2.0 equiv Cs_2CO_3, 80 °C, 16 h).

Building on this discovery, we set out to investigate whether the reaction in the more favorable solvents showed any differences with the previous DMSO-based system (Table 3). The catalyst loading as well as required equivalents of the base were investigated to determine if the reaction was distinct from the prior iteration. In the case of base loading, the experiments performed similarly with yield of product decreasing as the amount of base dropped below 2.0 equiv for both DMSO and 2-MeTHF, although more significantly for the latter solvent (entries 1−6).

Table 3. Investigation of Catalyst and Base Loading

entry	mol % Cu	equiv base	solvent	yield (%)[a]
1	20	2.0	DMSO	50
2	20	1.5	DMSO	46
3	20	1.0	DMSO	42
4	20	2.0	2-MeTHF	59
5	20	1.5	2-MeTHF	29
6	20	1.0	2-MeTHF	20
7	20	2.0	EtOAc	54
8	10	2.0	DMSO	50
9	10	2.0	2-MeTHF	48
10	5	2.0	DMSO	49
11[b]	5	2.0	2-MeTHF	50
12[c]	5	2.0	EtOAc	53

[a]Isolated yields (4.0 mmol 2-bromobenzaldehyde, 1.2 equiv EtO_2CCH_2NHAc, 80 °C, 16 h). [b]Reaction demonstrated on 5 g (20 mmol) scale. [c]Reaction demonstrated on 10 g (40 mmol) scale.

Furthermore, the reaction proceeded well with a reduced catalyst loading—down to 5 mol %— indicating that additional sustainability improvements were possible (compare entries 1, 4, 7−12). The transformation with 5 mol % catalyst in benign solvents was demonstrated to be very practical as 5 and 10 g scale experiments in 2-MeTHF and EtOAc, respectively, proceeded as expected to give the desired product in 50−53% isolated yield (Table 3, entries 11 and 12). Overall, the methodology performed in a similar fashion in the sustainable organic solvents as it had in the dipolar aprotic solvent DMSO, an encouraging finding. This discovery implies that substitution of dipolar aprotic solvents with greener variants should be possible for other intramolecular reactions with functionalities in favorable proximity to each other.

With the conditions refined, a variety of commercially available bromobenzaldehydes were combined with ethyl acetamidoacetate as coupling partner (Table 4). In each case, the unoptimized transformation produced similar yields of the desired indole-2-carboxylic ester when compared across the three solvents (A) DMSO, (B) 2-MeTHF, and (C) EtOAc (entries 1−7). There was no obvious difference in outcome with regard to electron-rich vs electron-poor substrates.

In addition to the formation of substituted indoles, some further heterocycles were realizable. Ethyl 1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxylate (Table 4, entry 8) was produced in both DMSO and 2-MeTHF, albeit in lower than expected yield (24−34%). Although not further investigated, the reduced output for these 7-aza-indole reactions was suspected to result from the absence of external ligand and coordination of copper with the pyridine moiety in the substrate or product.

Most importantly, 3-bromofuran aldehyde successfully participated in the 3-step transformation to efficiently produce the fused heterocycle ethyl 4*H*-furo[3,2-*b*]pyrrole-5-carboxylate in 50% isolated yield (Table 4, entry 9). As a compound under investigation for serious CNS disorders, including schizophrenia, pain, and neurodegeneration, this product was subsequently manufactured via a related method where the formyl group was added to a precursor, 3-bromofuran, and the synthesis telescoped over multiple steps to achieve greater sustainability efficiencies.[57]

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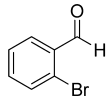
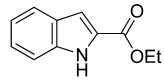
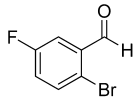
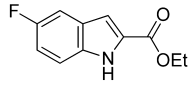
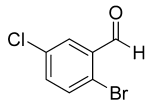
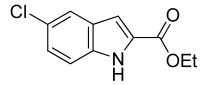
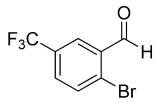
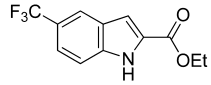
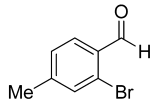
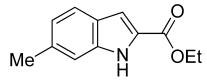
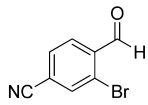
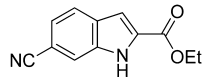
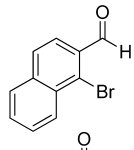
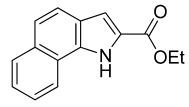
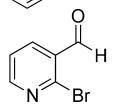
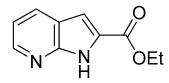
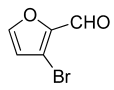
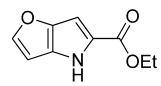
Table 4. Synthesis of Various Heterocycle-2-carboxylic Esters

Entry	Starting Material	Desired Product	Yield (%)[a]
1			A[b]: 51 B[b]: 59 C[b]: 54
2			A: 53 B: 43
3			A: 47 B: 45 C: 46
4			A: 44 B: 52
5			A: 41 B: 42
6			A: 53 B: 47
7			B: 41
8			A: 24 B: 34
9			B: 50

[a]Isolated yields (4.0 mmol bromoarylaldehyde, 1.2 equiv EtO_2CCH_2NHAc, 20 mol % CuI, 2.0 equiv Cs_2CO_3, 80 °C, 16 h). [b]Solvent designations: A = DMSO, B = 2-MeTHF, and C = EtOAc.

CONCLUSION

In summary, we have developed a greener synthesis of indoles and other fused heterocycles that improves on our previously reported copper-catalyzed reaction, free of external ligand. The significant improvement comes from the substitution of dipolar aprotic media with renewable solvents—2-MeTHF and EtOAc—that are derived from sustainable resources and obviate the need for excessive organic solvents and superfluous water during aqueous workup. Efficient access is enabled to a series of diverse indole-2-carboxylic esters and, most notably, the fused heterocycle ethyl 4*H*-furo[3,2-*b*]pyrrole-5-carboxylate, a promising compound for the treatment of serious CNS disorders. This work is encouraging for the exploration of greener solvent substitutions in other intramolecular systems where the positioning of complementary functionalities is similarly favorable.

ASSOCIATED CONTENT

Supporting Information

General procedure and characterization data of compounds prepared by the reported methodology. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ABBREVIATIONS

CH_3CN, acetonitrile; CNS, central nervous system; Cs_2CO_3, cesium carbonate; DMEDA, *N*,*N*′-dimethylethylenediamine; DMF, dimethylformamide; DMSO, dimethyl sulfoxide; EtOH, ethanol; EtO_2CCH_2NHAc, ethyl acetamidoacetate; EtOAc, ethyl acetate; MEK, methyl ethyl ketone; 2-MeTHF, 2-methyltetrahydrofuran; ND, none detected; NMP, *N*-methyl-2-pyrrolidone

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