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Iodine-catalyzed, one-pot, three-component aza-Friedel–Crafts reaction of electron-rich arenes with aldehyde/carbamate combinations

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ABSTRACT

lodine is shown to be an efficient catalyst for a one-step, three-component aza-Friedel–Crafts reaction of activated arenes or heteroarenes with benzyl or *tert*-butyl carbamates in combination with a wide variety of aldehydes in toluene under 'open-flask' and mild conditions. In the presence of 5 mol % of iodine in toluene at room temperature, the reaction gives the corresponding *N*-CBz or *N*-Boc protected α -branched amines, selectively, in good to excellent yields.

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An important structural motif, which is found in various natural products and drugs with well recognized pharmacological properties, is the α -branched amine skeleton.¹ A frequently used method for the synthesis of functionalized α -branched amine derivatives is the aza-Friedel–Crafts reaction (AFCR) between electron-rich aromatic/heteroaromatic compounds and imine derivatives.^{2,3} However, most of the reported methods are multi-step processes and require highly electrophilic imine acceptors such as those derived from glyoxalates,⁴ and trifluoroacetaldehyde.⁵ In contrast, less activated imine substrates, such as the imines of aromatic aldehydes, generally evolve according to a double Friedel–Crafts process to afford symmetrical triarylmethanes due to the intrinsic instability of the intermediate benzylamine under the acidic reaction conditions.⁶

Three-component AFCRs have become an efficient and powerful tool for the construction of the corresponding α -branched amines, diarylmethylamines, because of the fact that the desired products are formed in a one-pot reaction without isolation of the intermediates under standard reaction conditions.^{6b,7,8} However, most of the examples reported to date are limited to the reactions of indoles or 2-naphthols, amides or urea, and non-enolizable, most notably, aryl aldehydes.^{8–10} Furthermore, some of the reported methods suffer from disadvantages such as the use of expensive and corrosive reagents, high catalyst loading, long reaction times, strongly acidic conditions, low yields of products, and the use of microwave or ultrasonic irradiation.⁹ Therefore, to avoid these lim-

For initial optimization of the reaction conditions, 1,3,5-trimethoxybenzene (**1a**), benzaldehyde (**2a**), and benzyl carbamate (**3a**) were chosen as model substrates, using 10 mol % of I_2 as the catalyst. The solvent effect was also examined. The results are listed in Table 1. It was observed that when non-polar and weakly

itations, the development of methods utilizing aromatic and het-

eroaromatic systems, amine sources, aldehydes, easily available

catalysts with high catalytic activity, and short reaction times for

the preparation of diarylmethylamine derivatives is still desirable. Molecular iodine has been used as an efficient catalyst for sev-

eral chemical transformations.¹¹ As part of our interest in the

employment of molecular iodine as an alternative, simple, inexpensive, and less toxic reagent,¹² herein we report a highly efficient

one-pot, three-component aza-Friedel-Crafts reaction of electron-

rich arenes or heteroarenes, aldehydes, and benzyl or *tert*-butyl

carbamates under mild conditions (Scheme 1).

polar solvents such as toluene, CH_2Cl_2 , or THF were used, the reaction gave **4a** as the major product (80–81%) and only a trace amount of double-addition product **5a** (entries 1–3). The use of polar aprotic and polar protic solvents such as CH_3CN and CH_3OH , respectively, was less effective and lower product yields of 48–71% were obtained (entries 4, 5). It should be noted that

$$Ar - H + H_2NCO_2R + H + R^1 \xrightarrow{I_2 (5 \text{ mol}\%)} Ar + R^1$$

Scheme 1. I₂-catalyzed three-component aza-Friedel–Crafts reaction.

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Table 1

Model and optimization studies^a



^a Reaction conditions: **1a** (1 mmol), **2a** (1.1 mmol), **3a** (1 mmol), I₂, solvent (1 mL), room temperature.

^b Isolated yield.

^c No reaction based on TLC analysis.

symmetrical triarylmethane **5a** was obtained in 25% yield when the reaction was carried out in CH_3OH . This indicates accelerated ionization of the benzyl carbamate group by the polar protic solvent, resulting in the double-addition product. The reaction under neat conditions and stirring for 12 h (entry 6) gave the desired product **4a** in moderate yield (51%). From the solvent effect study, it was determined that toluene was the solvent of choice. We also investigated the influence of catalyst loading on the model reaction in toluene (entries 7–9). The results showed that the yield of the desired product **4a** increased slightly on lowering the catalyst loading to 5 mol % and the reaction was generally complete within 2 h at room temperature (entry 8).⁹ No side product was observed. A control reaction in the absence of iodine gave no products and the starting materials were recovered (entry 9).

The scope of the reaction under the optimized conditions was investigated by varying the aldehyde and carbamate components and results are summarized in Table 2.13 In the presence of 5 mol % of I₂, 1,3,5-trimethoxybenzene and benzyl or tert-butyl carbamate reacted with a number of aromatic aldehydes possessing either electron-withdrawing (F, Cl, Br, and NO₂) or electrondonating (OMe) substituents to give the corresponding N-protected diarylmethylamines 4a-f and 4h-m, selectively, in good to excellent yields (entries 1-7 and 9-14). Due to the low reactivity of 4-nitrobenzaldehyde, increasing the catalyst loading to 10 mol % led to a significant increase in the yield of **4e** as well as **4l** together with the formation of symmetric triarylmethane **5e** (entries 6 and 13). Furthermore, the corresponding α -branched amines **4g** and **4n** were obtained smoothly in good yields when 1,3,5-trimethoxybenzene and benzyl or tert-butyl carbamate were treated with cyclopentanecarbaldehyde (entries 8 and 15). From the results in Table 2, it should be noted that both benzyl and tert-butyl carbamates afforded good to excellent yields of the desired products 4a-n, however from the tert-butyl carbamates, there was a decrease in the formation of the double-addition adducts **5a-g**.

Encouraged by these results, we next investigated the threecomponent AFCR with an array of arenes as well as heteroarenes, aldehydes, and benzyl or *tert*-butyl carbamates. The results presented in Table 3 show that the reactions led to selective formation of α -branched amines **40–u** in moderate to high yields. The reaction of 1,2,4-trimethoxybenzene with benzaldehyde and *tert*-butyl carbamate gave the corresponding diarylmethylamine **40** and symmetrical triarylmethane **5h** in 57% and 15% yields, respectively

Table 2

 $I_2\text{-}\mathsf{catalyzed}$ reaction of arene 1a, benzyl or tert-butyl carbamates, and various aldehydes a



 a Reaction conditions: 1 (1 mmol), 2 (1.1 mmol), 3 (1 mmol), I_2 (5 mol %), toluene (1 mL), room temperature.

^b Isolated yield.

 c The reaction was carried out using I₂ (10 mol %) in toluene.

 $^{d}\,$ The reaction was carried out using I_2 (10 mol %) in THF.

(entry 1). Furthermore, 2-naphthol (**1c**) reacted efficiently with 4chlorobenzaldehyde and benzyl/*tert*-butyl carbamates to produce 1-carbamato-alkyl-2-naphthol derivatives **4p,q** in good yields (entries 2 and 3). It is noteworthy that compounds **4p,q** can be converted into important biologically active 1-aminomethyl-2-naphthol derivatives by carbamate hydrolysis.¹⁰ The three-component AFCR was also successfully applied to heteroaromatic compounds

Table 3

I2-catalyzed reaction of various arenes with aliphatic and aromatic aldehydes and benzyl or tert-butyl carbamate^a

						$H_2NCO_2R^2$ 3	NHCO ₂ F	R ² R ¹	
			Ar—H	+	2 R ¹ CHO	I ₂ (5 mol%) toluene, rt	Ar R ¹	+ Ar Ar	
			1b: 1,2,4-trimetl 1c: 2-naphthol 1d: 2-methylfura 1e: 2-ethylfuran 1f: 2-methylthio	hoxybenzene an phene		3a ; R ² = Bn 3b ; R ² = <i>t</i> -Bu	4	5	
Entry	Ar-H	\mathbb{R}^1	R ²	Time (h)			Prod	ucts yield ^b (%)	
1	1b	C ₆ H ₅	t-Bu	2	MeO	OMe NHCO ₂ t-Bu	4o (57)	MeO OMe OMe	5h (15)
2	1c	4-ClC ₆ H ₄	Bn	18	OH	NHCO ₂ Bn	4p (74) ^{<i>c</i>}	OH Ph OH OH	5i (-) ^c
3	1c	4-CIC ₆ H ₄	t-Bu	24	OH	NHCO ₂ t-Bu	4q (62) ^c	OH Ph OH OH	5i (-) ^c
4 5	1d 1d	$\begin{array}{c} C_6H_5\\ C_6H_5 \end{array}$	t-Bu t-Bu	24 6	H ₃ C	NHCO ₂ t-Bu	4r (52) 4r (61) ^{<i>d</i>}	Ph O H ₃ C	5j (19) 5j (38) ^d
6 7	1e 1e	C_6H_5 C_6H_5	t-Bu t-Bu	2 2	H₃CH₂	NHCO ₂ t-Bu	4s (90) 4s (65)e	Ph Ph CH ₂ CH ₂ CH	5k (−) 5 k (7) ^e
8 9	1f 1f	C ₆ H ₅ C ₆ H ₅	t-Bu t-Bu	2 2	H ₃ C	NHCO ₂ t-Bu	4t (27) 4t (40) ^e	Ph S H ₃ C	5l (-) 5l (-) ^e
10	1f	(CH ₃) ₂ CH	t-Bu	2	H ₃ C	NHCO ₂ t-Bu	4u (48) ^f	H ₃ C	5m (–) ^f

^a Reaction conditions: 1 (1 mmol), 2 (1.1 mmol), 3 (1 mmol), I_2 (5 mol %), toluene (1 mL), room temperature.

^b Isolated yield.

^c The reaction was carried out at using I₂ (10 mol %) in CH₃CN at 60 °C.

 d The reaction was carried out using I₂ (10 mol %) in THF (1 mL) at room temperature.

 $^{\rm e}$ The reaction was carried out using I₂ (5 mol %) in THF (1 mL) at room temperature.

 $^{\rm f}~$ The reaction was carried out using I_2 (20 mol %) in toluene (1 mL) at room temperature.

such as 2-methylfuran (1d), 2-ethylfuran (1e), and 2-methylthiophene (1f) with benzaldehyde and *tert*-butyl carbamate to afford the functionalized α -branched amines **4r–t** in moderate to high yields (entries 4–9). Finally, we tested the efficiency of this reaction with the aliphatic aldehyde, isobutyraldehyde (entry 10): with 2-methylthiophene and *tert*-butyl carbamate, the substrates were converted smoothly into the desired product.

In summary, we have demonstrated an efficient iodine-catalyzed, one-pot, three-component AFCR of arenes/heteroarenes, benzyl/*tert*-butyl carbamate and a wide variety of aldehydes in toluene under 'open-flask' and mild conditions. Typically, the corresponding *N*-Cbz or *N*-Boc protected α -branched amines were

obtained, selectively, in good to excellent yields. The use of mild reaction conditions, low catalytic loading, and easy removal of the N-protective group¹⁴, and one-step synthesis are advantages of the present procedure. Further investigations on the scope and limitations of this reaction are in progress.

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- Typical experimental procedure: To a toluene solution (1 mL) of arene 1 13 (1.0 mmol), aldehyde 2 (1.1 mmol), and carbamate 3 in a test-tube open to air at room temperature was added molecular I_2 (0.05 mmol, 5 mol %). The reaction was stirred until completion (TLC analysis). The mixture was quenched with aqueous $Na_2S_2O_3$ (10 mL) and extracted with CH_2Cl_2 $(2 \times 10 \text{ mL})$. The combined organic layer was washed with brine (10 mL), dried over anhydrous MgSO4, concentrated, and purified by radial chromatography (hexanes/EtOAc as eluent) to give 4 as the major product and **5** as the minor product. Spectral data for **4a**: ¹H NMR (400 MHz, CDCl₃): δ 7.14–7.44 (10H, m), 6.69 (1H, d, J = 10.1 Hz), 6.52 (1H, d, J = 10.1 Hz), 6.15 (2H, s) 5.19 (1H, d, J = 12.1 Hz), 5.12 (1H, d, J = 12.1 Hz), 3.82 (3H, s), 3.78 (6H, s); ¹³C NMR (100 MHz, CDCl₃): δ 160.1, 158.6, 156.3, 143.0, 138.6, 128.5, 128.3, 127.9, 126.3, 126.0, 110.8, 91.3, 66.8, 55.9, 55.4, 48.9; IR (Nujol): v_{max} 3444, 1721, 1608, 1593, 1497 cm⁻¹; HRMS (EI) calcd for C₂₄H₂₅NO₅ 407.1727, found: 407.1727. **5a**: ¹H NMR (400 MHz, CDCl₃): δ 7.15 (2H, t, J = 7.4 Hz), 7.06 (3H, d, I = 4.8 Hz), 6.22 (1H, s), 6.12 (4H, s), 3.79 (6H, s), 3.50 (12H, s); ¹³C NMR (100 MHz, CDCl₃): δ 159.9, 159.2, 145.7, 127.8, 127.1, 124.2, 114.4, 91.9, 56.2, 55.2, 37.1; IR (Nujol): v_{max} 1591, 1455, 1415, 1230, 1204; HRMS (ESI-TOF) calcd for C25H28O6Na 447.1784, found: 447.1760.
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