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Synthesis of Isoindolo[2,1-*a*]quinazoline, Isoindolo[2,1-*a*]pyrrolo[2,1-*c*]quinoxalinone, and Indolo[1,2-*a*]isoindolo[1,2-*c*]quinoxalinone Derivatives in a Deep Eutectic Solvent

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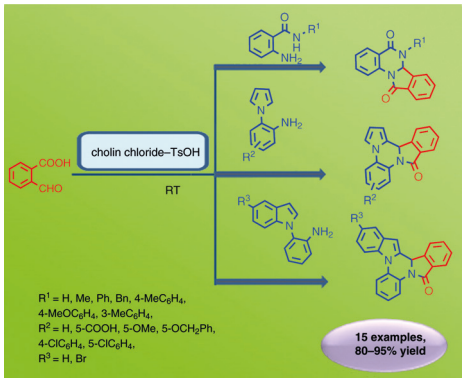

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Abstract 2-Formylbenzoic acid reacts with various derivatives of 2-aminobenzamide, 2-(1*H*-pyrrol-1-yl)aniline or 2-(1*H*-indol-1-yl)aniline in a deep eutectic solvent to give the corresponding derivatives of 6,6a-dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione, isoindolo[2,1-*a*]pyrrolo[2,1-*c*]quinoxalin-10(14b*H*)-one, and indolo[1,2-*a*]isoindolo[1,2-*c*]quinoxalin-11(15b*H*)-one, respectively . This protocol is operationally simple, mild, and efficient.

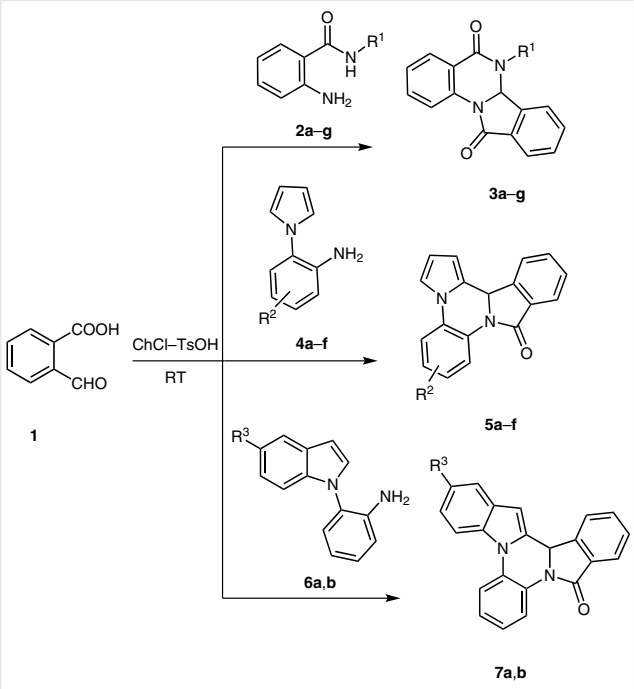
Key words eutectics, formylbenzoic acid, isoindoloquinazolinediones, isoindolopyrroloquinoxalinones, indoloisoindoloquinoxalinones derivatives, aminobenzamides

The isoindolone fragment forms part of the skeletal framework of many synthetic or naturally occurring biologically active products.[1–8] Isoindolo[2,1-*a*]quinazoline-5,11-dione derivatives have been reported to exhibit various biological activities, including inhibition of tumor necrosis factor-α, which plays a major role in the treatment of rheumatoid arthritis, Crohn's disease, and ulcerative colitis.[9] Reported methods for the synthesis of isoindolo[2,1-*a*]-quinazoline derivatives include reactions catalyzed by acetic acid,[10,11] montmorillonite K10,[9] β-cyclodextrin,[12] *Saccharomyces cerevisiae*,[13] CuO nanoparticles,[14] iodine in an ionic liquid,[15,16] $SnCl_2{\cdot}2H_2O$,[17] or Fe in acetic acid.[18] Pyrrolo[1,2-*a*]quinoxalines have been prepared by a Mannich protocol,[19,20] a 1,3-dipolar cycloaddition reaction strategy,[21] a base-catalyzed approach,[22] visible light induced photoredox catalysis,[23] a modified Pictet–Spengler reaction catalyzed by TsOH with benzotriazole as an additive,[24] or intramolecular amidoalkylation–cyclization,[25] and by phase-transfer-catalyzed or trimethylsilyl cyanide catalyzed routes for the synthesis of their Reissert analogues.[26] Methods for preparing indoloquinoxalines include a photocyclization strategy,[27] ruthenium-catalyzed C–H bond activation and cyclization,[28] and a modified Pictet–Spengler reaction catalyzed by TsOH with benzotriazole as an additive.[24] The synthesis of imidazoquinoxalines through a Pictet–Spengler reaction on a solid phase has been reported.[29] However, these protocols suffer from various drawbacks, such as extended reaction times in the range of 7–15 hours,[9,14,16,17] low to moderate yields,[11] or the use of organic solvents such as EtOH,[9,17] acetic acid,[10,11,18] THF,[13,24] or toluene.[24]

In recent years, deep eutectic solvents (DESs) have emerged as promising green solvents. These are preferred to conventional organic solvents because they are nonvolatile, nonflammable, nontoxic, biodegradable, inexpensive, recyclable, and have excellent solvation properties.[30–36] A DES is usually composed of a mixture of a quaternary ammonium salt and a hydrogen-bond donor. Several DESs with choline chloride (ChCl) as the quaternary ammonium salt component have been developed.

Here, we report an environmentally benign synthesis of derivatives of 6,6a-dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione **3a–g**, isoindolo[2,1-*a*]pyrrolo[2,1-*c*]quinoxalin-10(14b*H*)-one **5a–f**, and indolo[1,2-*a*]isoindolo[1,2-c]quinoxalin-11(15bH)-one (**7a**,**b**) in a deep eutectic solvent prepared from *p*-toluenesulfonic acid and choline chloride (Scheme 1).

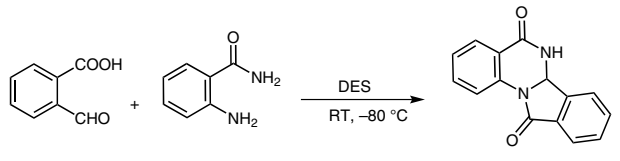
The reaction between 2-formylbenzoic acid (**1**) and 2-aminobenzamide (**2a**) in DES as the reaction medium was studied under various conditions (Table 1). The reaction failed at room temperature when ChCl–oxalic acid or ChCl–malonic acid was used as the DES (Table 1, entries 1 and 5). In these cases, heating to 80 °C for one hour was necessary



Scheme 1

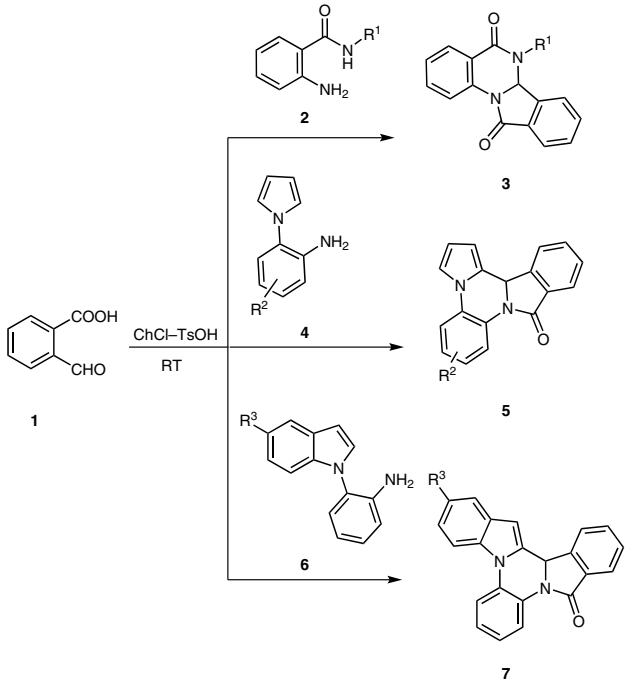
for complete consumption of the starting materials (entries 4 and 8). The same reaction proceeded at room temperature within 15 minutes when a DES consisting of choline chloride and TsOH was used (entry 9). This was therefore established as the optimal protocol. The reaction mixture, on dilution with a small amount of water, afforded a solid product that could be isolated by simple filtration. The isolated product was highly pure, as evident from TLC analysis, and was identified as isoindolo[2,1-*a*]quinazoline (**3a**) on the basis of its ^{1}H NMR spectrum, which was identical to that reported.[10] We obtained **3a** in 95% yield.

Table 1 Screening of DESs



Entry	DES	Time (h)	Temp (°C)	Yield (%)
1	ChCl–oxalic acid	12	r.t.	no reaction
2		10	40	traces
3		8	60	60
4		1	80	85
5	ChCl–malonic acid	12	r.t.	no reaction
6		10	40	traces
7		8	60	55
8		1	80	90
9	ChCl–TsOH	0.25	r.t.	95

Table 2 Reactions of 2-Formylbenzoic Acid with 2-Aminobenzamides, 2-(1*H*-pyrrol-1-yl)anilines or 2-(1*H*-indol-1-yl)anilines in the Deep Eutectic Solvent[a]



Entry	Substrate	Product	Time (h)	Yield[b] (%)
1	**2a**; R^1 = H	**3a**	0.25	95[c]
2	**2b**; R^1 = Me	**3b**	1	88
3	**2c**; R^1 = Ph	**3c**	1	87
4	**2d**; R^1 = Bn	**3d**	1	84
5	**2e**; R^1 = 4-Tol	**3e**	1	80
6	**2f**; R^1 = 4-MeOC$_6$H$_4$	**3f**	1	81
7	**2g**; R^1 = 3-Tol	**3g**	1	88
8	**4a**; R^2 = H	**5a**	0.75	90
9	**4b**; R^2 = 5-CO$_2$H	**5b**	3.5	85
10	**4c**; R^2 = 5-OMe	**5c**	0.33	90
11	**4d**; R^2 = 5-OBn	**5d**	0.42	88
12	**4e**; R^2 = 4-ClC$_6$H$_4$	**5e**	5	80
13	**4f**; R^2 = 5-ClC$_6$H$_4$	**5f**	5	82
14	**6a**; R^3 = H	**7a**	2	90
15	**6b**; R^2 = Br	**7b**	2	92

[a] Reaction conditions: 2-formylbenzoic acid (**1**; 1 mmol), amine **2**, **4**, or **6** (1 mmol), ChCl–TosOH DES (1.5 g), RT.
[b] Isolated yield after crystallization.
[c] This compound required no crystallization.

Next, we evaluated the scope of the protocol by carrying out the reactions of 2-formylbenzoic acid (**1**) with various 2-aminobenzamide derivatives **2** (Table 2, entries 1–7). A wide range of 2-aminobenzamide derivatives **2** gave the corresponding isoindolo[2,1-*a*]quinazolines **3a–g** within one hour. All the synthesized products (apart from **3a**) were crystallized from ethanol to remove traces of impurities. We were also able to extend the scope of this protocol to the synthesis of isoindolo[2,1-*a*]pyrrolo[2,1-*c*]quinoxalin-10(14b*H*)-ones **5a–f** by the reaction of 2-formylbenzoic acid (**1**) with 2-(1*H*-pyrrol-1-yl)aniline derivatives **4**. The protocol tolerated 2-(1*H*-pyrrol-1-yl)aniline derivatives **4** with electron-donating or electron-withdrawing groups (entries 9–13). The reaction between 2-formylbenzoic acid and 2-(1H-pyrrol-1-yl)aniline derivatives having electron-withdrawing groups (entries 9, 12, and 13) took longer for completion of the reaction. The same reaction strategy was successfully applied to the synthesis of indolo[1,2-*a*]isoindolo[1,2-*c*]quinoxalin-11(15b*H*)-one derivatives **7a**,**b** through the reaction of 2-formylbenzoic acid (**1**) with 2-(1*H*-indol-1-yl)aniline derivatives **6a**,**b** (entries 14 and 15).

A significant feature of this protocol lies in the recyclability of DESs. The DES used in the model reaction of 2-formylbenzoic acid (**1**) with 2-aminobenzamide (**2a**) was recovered as described in the Supporting Information and reused in two further runs of the reaction to give product **3a** in yields of 91% and 88% from the second and third cycle, respectively (Table 3).

Table 3 Reusability of the DES

Entry	Reaction cycle	Yield[a] (%)
1	first (fresh)	95
2	second	91
3	third	88

[a] Isolated yield.

In conclusion, we have developed a highly efficient, one-pot, green protocol for the synthesis of derivatives of 6,6a-dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione, isoindolo-[2,1-*a*]pyrrolo[2,1-*c*]quinoxalin-10(14b*H*)-one, and indolo-[1,2-*a*]isoindolo[1,2-*c*]quinoxalin-11(15b*H*)-one.[37]

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(37) **6,6a-Dihydroisoindolo[2,1-*a*]quinazoline-5,11-diones 3a–g, Isoindolo[2,1-*a*]pyrrolo[2,1-*c*]quinoxalin-10(14b*H*)-ones 5a–f, and Indolo[1,2-*a*]isoindolo[1,2-*c*]quinoxalin-11(15b*H*)-ones 7a,b; General Procedure**

To a mixture of 2-formylbenzoic acid (**1**; 1 mmol) and the appropriate amine **2**, **4**, or **6** (1 mmol) was added the DES (1.5 g), prepared from ChCl and TsOH.[31] The resulting mixture was stirred at r.t. until the starting materials were completely consumed (TLC). The reaction mass was then diluted with H_2O (5 mL), and the desired product, obtained as a precipitate, was isolated by filtration and crystallized from the appropriate solvent. The filtrate was evaporated under vacuum at 70 °C for 2 h, and the residual DES was reused in further reaction cycles.

6,6a-Dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione (3a)

White solid; yield: 237 mg (95%); ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.406 (s, 1 H), 8.089 (d, *J* = 7.5 Hz, 1 H), 7.983 (d, *J* = 7 Hz, 1 H), 7.898 (d, *J* = 7 Hz, 2 H), 7.801 (t, *J* = 7 Hz, 1 H), 7.724–7.688 (m, 2 H), 7.361 (t, *J* = 7 Hz, 1 H), 6.526 (s, 1 H).