One-Pot, Three-Component Synthesis of Novel Spiro[3*H*-indole-3,2′-thiazolidine]-2,4′(1*H*)-diones in an Ionic Liquid as a Reusable Reaction Media

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A facile one-pot, three-component protocol for the synthesis of novel spiro[3*H*-indole-3,2′-thiazolidine]-2,4′(1*H*)-diones by condensing 1*H*-indole-2,3-diones, 4*H*-1,2,4-triazol-4-amine and 2-sulfanylpropanoic acid in [bmim]PF_6 (1-butyl-3-methyl-1*H*-imidazolium hexafluorophosphate) as a recyclable ionic-liquid solvent gave good to excellent yields in the absence of any catalyst (*Scheme 1* and *Table 2*). The advantages of this protocol over conventional methods are the mild reaction conditions, the high product yields, a shorter reaction time, as well as the eco-friendly conditions.

Introduction. – In recent years, the development of multicomponent reactions (MCRs) has become a powerful protocol in organic synthesis and medicinal chemistry [1]. They have been established as one of the efficient as well as powerful ways for the synthesis of biologically active heterocycles [2]. Imines are excellent reaction intermediates that can act as nucleophiles/electrophiles. Imine-based multicomponent reactions allow the facile and selective construction of highly functionalized molecules with diverse and complex structures as well as small and drug-like heterocyclic compounds from readily available starting materials in a single synthetic operation [3]. Hence, such reactions provide a valuable synthetic tool for the synthesis of heterocycles with biological value.

As a part of our continuing efforts on the development of new methodologies for the synthesis of bioactive heterocycles by employing eco-friendly tools [4], considering the significance of the ionic liquid and need to develop a rapid as well as facile synthetic procedure for spiro[3*H*-indole-3,2′-thiazolidine]-2,4′(1*H*)-diones **4**, we report herein the synthesis of the latter in excellent yields by employing a convenient one-pot, three-component cyclocondensation of 1*H*-indole-2,3-diones **1**, 4*H*-1,2,4-triazol-4-amine (**2**) and 2-sulfanylpropanoic acid (**3**) in [bmim]PF_6 (1-butyl-3-methyl-1*H*-imidazolium hexafluorophosphate), an ionic liquid, in the absence of any catalyst.

Results and Discussion. – To optimize the reaction conditions of the synthesis of spiro[3*H*-indole-3,2′-thiazolidine]-2,4′(1*H*)-diones **4**, we first investigated a two-step synthesis as well as the one-pot, three-component reaction of 1*H*-indole-2,3-dione (**1a**), 4*H*-1,2,4-triazol-4-amine (**2**), and 2-sulfanylpropanoic acid (**3**) as a model reaction in various solvents such as benzene, toluene, acetic acid, and ionic liquid to afford the functionalized spiro[indole-thiazolidine]-dione **4a** (*Table 1*; *Scheme 1*). Thus, the yield of **4a** increased remarkably in ionic liquid with the increase of the temperature up to

Table 1. *Optimization of the Reaction Conditions for the Synthesis of Compound* **4a**

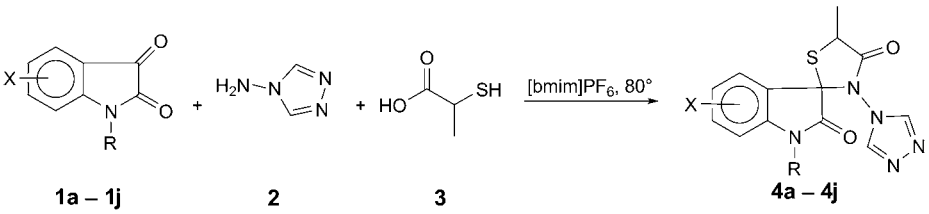
Solvent	Temp. [°]	Time [h]	Yield [%][a])
[bmim]PF_6	r.t.	10	50
[bmim]PF_6	60	6	75
[bmim]PF_6	70	5	80
[bmim]PF_6	80	4	92
[bmim]PF_6	90	4	92
Benzene	reflux	10	55
Toluene	reflux	9	68
AcOH	reflux	7	69
Toluene[b])	reflux	5 + 7	53
Toluene[c])	reflux	5 + 7	57

[a]) Yields refer to pure isolated **4a**. [b]) The intermediate *Schiff* base was isolated (two step). [c]) The intermediate *Schiff* base was not isolated (two step).

80°. The best result, *i.e.*, an excellent yield in a shorter reaction time was obtained in [bmim]PF_6, as ionic liquid because of the hydrophobic nature of the latter, which creates a micro-environment to drive the equilibrium by extruding H_2O out of the ionic liquid phase resulting in a higher conversion.

Subsequently, 5′-methyl-3′-(4*H*-1,2,4-triazol-4-yl)spiro[3*H*-indole-3,2′-thiazolidine]-2,4′(1*H*)-diones **4a**–**4j** were synthesized in exellent yields (89–93%) by the reaction of 1*H*-indole-2,3-diones **1a**–**1j**, triazol-amine **2**, and acid **3** in [bmim]PF_6 under N_2 at 80 ± 2° in the absence of any further catalyst (*Scheme 1* and *Table 2*).

Scheme 1. *Ionic-Liquid-Mediated One-Pot, Three-Component Synthesis of Spiro[3*H*-indole-3,2′-thiazolidine]-2,4′(1*H*)-diones* **4a**–**4j**. For R and X, see *Table 2.*



1a – 1j **2** **3** **4a – 4j**

For comparison, the spiro[3*H*-indole-3,2′-thiazolidine]-2,4′(1*H*)-diones **4** were also synthesized by conventional heating in dry toluene *via* the *Schiff* bases 1,3-dihydro-3-[(4*H*-1,2,4-triazol-4-yl)imino]-2*H*-indol-2-ones **5** (*cf.* below, *Scheme 2*), which were prepared by the reaction of **1a**–**1j** and **2** and then isolated. In the second step, the *Schiff* bases were treated with **3** to give **4a**–**4j** in 51–56% yields. Alternatively, **4a**–**4j** were synthesized in poor to moderate yields (53–61%) under the same conditions but without isolating the *Schiff* bases, the latter being cyclized *in situ* with **3**.

The mechanism for the described reaction, exemplified for **4a** involves the initial *in situ* generation of 1,3-dihydro-3-imino-2*H*-indole-2-one **5a** by condensation of **1a** and **2**. This event is followed by the nucleophilic attack of the sulfanyl group of **3** at the

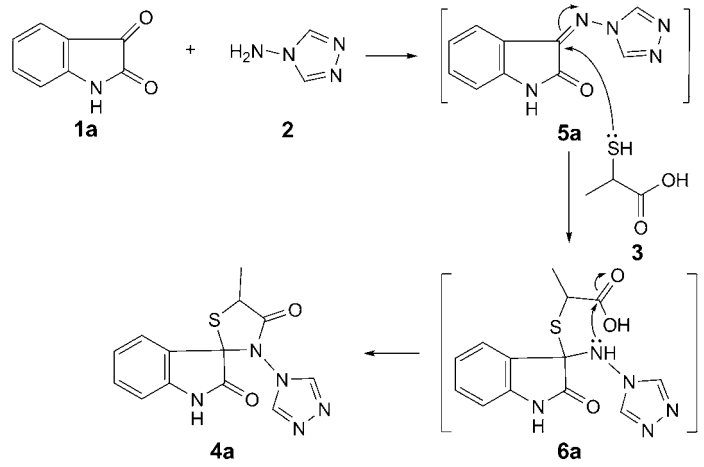
Table 2. *Ionic Liquid-Mediated Synthesis of Spiro[3*H*-indole-3,2′-thiazolidine]-2,4′(1*H*)-diones* **4a**–**4j**[a])

Product	R	X	Time [h]	Yield [%][b])	M.p. [°]
4a	H	H	4	92	163–165
4b	H	5-Cl	5	93	116–118
4c	H	5-F	5	93	136–138
4d	Ac	H	4	91	226–228
4e	Me	H	6	92	239–241
4f	Et_2NCH_2	H	5	89	176–178
4g	Me_2NCH_2	H	5	90	167–169
4h	Bn	H	4	92	209–211
4i	Me	5-Cl	5	92	147–149
4j	piperidin-1-ylmethyl	H	4	91	223–225

[a]) Reaction conditions: 1*H*-indole-2,3-dione **1** (1.0 mmol), 4*H*-1,2,4-triazol-4-amine (**2**; 1.0 mmol), 2-sulfanylpropanoic acid (**3**; 1.2 mmol), and [bmim]PF_6 (5.0 ml), TLC monitoring. [b]) Yield after purification.

imino-substituted C(3) to give intermediate **6a** [5], which undergoes cyclocondensation by lactam formation to yield **4a** (*Scheme 2*).

Scheme 2. *Mechanistic Pathway*



The structures of the products **4a**–**4j** were characterized unambiguously by analytical and spectroscopic studies. The IR spectrum of compound **4a** showed absorption bands at 1710 and 1690 cm^{-1} due to C=O groups of the thiazolidinone and oxindole moiety, respectively. The broad peak at 3190 cm^{-1} indicated the presence of an NH group in **4a**, while the intense peak at 1615 cm^{-1} was typical for the presence of C=N moieties. An absorption band at 748 cm^{-1} was attributed to a C–S–C linkage. Due to the presence of two stereogenic centers (C(3) and C(5′)), the compounds **4a**–**4j** exist in two diastereoisomeric forms, in a ratio of 3:1 for **4a** (by ^{1}H-NMR), exhibiting two sets of signals in the ^{1}H-NMR spectra for H–C(5′), Me–C(5′) and the NH group

(when present). However, the signals of the aromatic H-atoms could not be resolved because of their complex *m* pattern. This is exemplified by the ^{1}H-NMR spectrum of **4a** with 2 *d* at δ(H) 1.59 and 1.81 ($J = 6.9$ and 7.2 Hz) due to Me–C(5′), 2 *q* at δ(H) 4.37 and 4.16 due to H–C(5′), 2 *s* at δ(H) 9.99 and 10.42 due to the NH group, and 2 *s* at δ(H) 8.24 and 8.31 due to the triazole moiety. In the ^{13}C-NMR spectrum of **4a**, the peak at δ(C) 62.7 indicated the presence of a spiro C-atom, the C=O groups of the oxindole and thiazolidinone moiety resonated at δ(C) 168.0 and 177.5, respectively, C(5′) and *Me*–C(5′) appeared at δ(C) 42.3 and 18.0, respectively, and the signals at δ(C) 148.0 and 149.1 were attributable to C(3) and C(5) of the triazole moiety. The mass spectrum of **4a** displayed a distinguished peak at *m*/*z* 301.3, which further supported the formation of a spiro compound. The spiro[indole-thiazolidine]dione derivatives prepared by the conventional method had the same analytical and spectral data.

We also studied the reactivity of the recycled ionic liquid for the production of **4a** (*Table 3*): After two recycles, the yield of **4a** had decreased, yet the ionic liquid could be reused with significant success. Therefore, the ionic-liquid-mediated synthesis is an excellent approach for the synthesis of the title compounds and superior to the reaction in conventional reaction media.

Table 3. *Studies on the Recovery and Reuse of [bmim]PF_6 for the Production of* **4a**[a])

Recycle	Time [h]	Temperature [°]	Yield [%][b])	Recovered [bmim]PF_6 [*w*/*w*-%]
Fresh	4	80	92	98
1	4	80	89	95
2	4	80	87	93

[a]) Reaction conditions: **1a** (1.0 mmol), **2** (1.0 mmol), and **3** (1.2 mmol); 5.0 ml of ionic liquid [bmim]PF_6 was used for the first run. [b]) Yield of **4a** after purification.

In conclusion, we demonstrated an efficient, facile, one-pot, three-component ionic-liquid-mediated, mild and high-yielding methodology for the synthesis of novel spiro[3*H*-indole-3,2′-thiazolidine]-2,4′(1*H*)-diones with shorter reaction time as compared to the conventional heating method. The use of a ionic liquid led to a higher performance with the advantage that the ionic liquid could be recycled and reused without substantial loss of its activity. The significance of this approach consists of its environmentally acceptable conditions by the reduced use of volatile organic solvents, the simplicity of the process, excellent yields, mild conditions, and low costs.

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Experimental Part

General. Commercially available (*Acros Organics*) 4*H*-1,2,4-triazol-4-amine (**2**), 2-sulfanylpropanoic acid (**3**), and [bmim]PF_6 (1-butyl-3-methyl-1*H*-imidazolium hexafluorophosphate) were used without further purification. The 1*H*-indole-2,3-dione (**1a**) and its derivatives (starting material **1**) were prepared according to [6]. M.p.: *Gallenkamp* melting-point apparatus; in open glass capillaries; uncorrected. IR Spectra: *FT-IR-8400S-Shimadzu* spectrometer; in KBr; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Jeol* spectrometer; at 300 and 75 MHz, resp.; in (D_6)DMSO/$CDCl_3$; δ in ppm rel. to Me_4Si as

internal standard, *J* in Hz. MS*: Waters-Xevo-Q-TOF* instrument, equipped with an ASAP (atomspheric solids analysis probe). Elemental analyses (C, H, and N): *Vario-EL-III* analyzer.

Typical Experimental Procedure for the Synthesis of Compounds **4a**–**4j** (exemplified with **4a**). A soln. of 1*H*-indole-2,3-dione (**1a**; 1.0 mmol), 4*H*-1,2,4-triazol-4-amine (**2**; 1.0 mmol), 2-sulfanylpropanoic acid (**3**; 1.2 mmol), and [bmim]PF_6 (5.0 ml) stirred magnetically at $80 \pm 2°$ under N_2 (monitoring by TLC (petroleum ether/AcOEt 4:1, visualization by I_2 vapor)). After completion of reaction as evidenced by TLC, the mixture was cooled to r.t., neutralized with 10% aq. $NaHCO_3$ soln., and extracted with AcOEt (3×10 ml). The solvent was evaporated, the pasty mass thus obtained extracted with Et_2O (3×10 ml), the extract dried (Na_2SO_4), the Et_2O distilled off, and the residual product purified by crystallization from EtOH: **4a** (92%).

Recovery of the Ionic Liquid [bmim]PF_6. After completion of the reaction, the reaction mixture was poured into ice water (instead of cooling and washing with $NaHCO_3$ soln. followed by extraction), and the product was filtered off. The filtrate was extracted with AcOEt to recover unreacted reactants, and the aq. layer was subjected to evaporation of H_2O to get a viscous liquid which, on cooling, gave the ionic liquid. The ionic-liquid was washed with H_2O (3×10 ml) and kept for 2 h at 80–85° under reduced pressure. This ionic liquid was used twice in recycling experiments (*Table 3*).

*5′-Methyl-3′-(4*H*-1,2,4-triazol-4-yl)spiro[3*H*-indole-3,2′(1*H*)-thiazolidine]-2,4′(1*H*)-dione* (**4a**). Yellowish white solid. M.p. 163–165°. IR: 3190 (–NH), 1710 (C=O), 1690 (C=O), 1615 (C=N), 748 (C–S–C). ^{1}H-NMR (diastereoisomer ratio 3:1): 1.59, 1.81 (2 *d*, $J = 6.9$ and 7.2, Me–C(5′)); 4.37, 4.16 (2 *q*, $J = 6.9$ and 7.2, H–C(5′)); 6.85 (*d*, $J = 7.5$, 1 arom. H); 7.04 (*t*, $J = 7.5$, 1 arom. H); 7.25 (*t*, $J = 7.8$, 1 arom. H); 7.35 (*d*, $J = 7.5$, 1 arom. H); 8.24, 8.31 (2 *s*, CH triazole); 9.99, 10.42 (2br. *s*, NH, D_2O exchangeable). ^{13}C-NMR: 18.0; 42.3; 62.7; 110.6; 122.6; 125.3; 126.9; 130.6; 141.8; 148.0; 149.1; 168.0; 177.5. MS: 301.3. Anal. calc. for $C_{13}H_{11}N_5O_2S$: C 51.78, H 3.65, N 23.23; found: C 51.89, H 3.58, N 23.31.

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