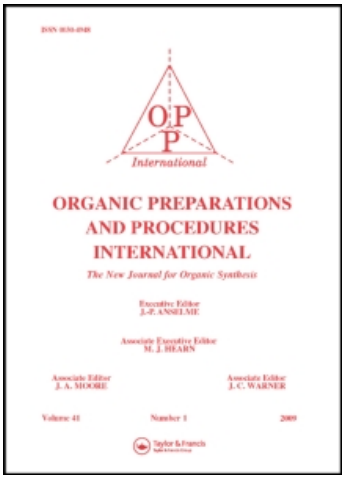

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Preparation of 4,6-Diarylindazole Derivatives in Ionic Liquid under Solvent-free Conditions

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Preparation of 4,6-Diarylindazole Derivatives in Ionic Liquid under Solvent-free Conditions

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Ionic liquids have been the subject of considerable current interest as environmentally benign reaction media in organic synthesis because of their unique properties of non-volatility, non-flammability, recyclability, and ability to dissolve a wide range of organic and inorganic compounds.[1–3] Ionic liquids are also thermally stable, have negligible vapor pressure and increased reaction rates, show selectivity and a tendency to immobilize starting materials and catalysts. Ionic liquids can play a significant role in controlling reactions as solvents or catalysts[4] and have been applied in various organic reactions,[5,6] such as the Friedel-Crafts,[7] the Diels-Alder[8,9] and Biginelli reactions,[10] the Beckmann rearrangement,[11,12] Michael addition[13] and other reactions.[14–16]

Among the new transformations, cyclocondensation reactions are attractive methodologies for the synthesis of heterocyclic compounds.[17] Indazole derivatives exhibit anti-inflammatory,[18] anti-depressant,[19] anti-arthritic,[20] anti-tumor[21] and analgesic[22] activities. Most of the methods to prepare indazoles proceed from benzene derivatives on which the pyrazole moiety is attached by ring closure.[21] We report a convenient synthesis of indazole derivatives from cyclohexenone derivatives in ionic liquid media.

A mixture of chalcone with ethyl acetoacetate and 1-butyl-3-methylimidazo liumbromide ([bmim]Br) was stirred at room temperature for the period of times shown in *Table 1*. The reaction mixture was then extracted with ether and the product was recrystallyzed from ethanol. The best results were obtained with a ratio of [1:1:0.7] mmols of chalcone, ethyl acetoacetate, [bmim]Br. Electron-withdrawing groups on phenyl rings led to shorter reaction times than electron-donating groups.

The present procedure catalyzed by a simple ionic liquid, [bmim]Br, provides an efficient and general methodology for Robinson Annulations. This method has the advantages

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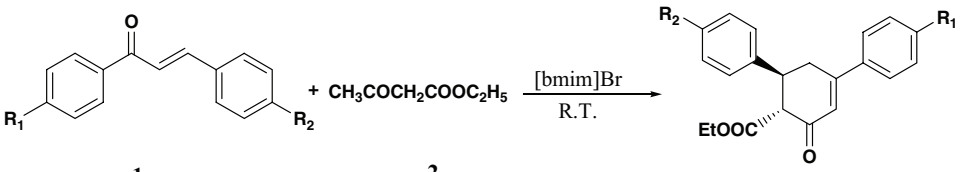
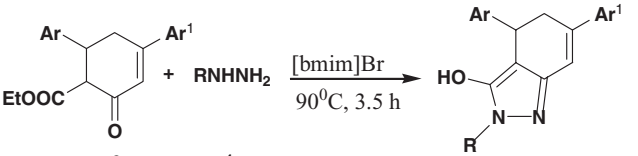


1 2 3

a) $R_1 = R_2 = H$; b) $R_1 = Cl$, $R_2 = H$; c) $R_1 = H$, $R_2 = Me$; d) $R_1 = Cl$, $R_2 = Me$; e) $R_1 = H$, $R_2 = Br$; f) $R_1 = Cl$, $R_2 = Br$; g) $R_1 = H$, $R_2 = NO_2$; h) $R_1 = Cl$, $R_2 = NO_2$

of shorter reaction times and higher yields compared to another representative method, catalyzed by K_2CO_3 (*Table 1*).[23]

Treatment of cyclohexenones (**3a**-**h**) with hydrazine hydrate or phenylhydrazine in [bmim]Br as solvent and catalyst at 90°C for 3.5 h produced indazole derivatives. The results are given in *Table 2*. The conditions led to shorter reaction times and higher yields compared with another representative method in which acetic acid was used as catalyst (*Table 2*).[25]



3 4 5

a) R = H, Ar = $Ar^1 = C_6H_5$; b) R = H, Ar = C_6H_5, Ar^1 = 4-Cl-C_6H_4; c) R = H, Ar = 4-Me-C_6H_4, $Ar^1 = C_6H_5$; d)R = H, Ar = 4-Me-C_6H_4, Ar^1 = 4-Cl-C_6H_4; e)R = H, Ar = 4-Br-C_6H_4, $Ar^1 = C_6H_5$; f)R = H, Ar = 4-Br-C_6H_4, Ar^1 = 4-Cl-C_6H_4; g) R = H, Ar = 4-NO_2-C_6H_4, $Ar^1 = C_6H_5$; h) R = H, Ar = 4-NO_2-C_6H_4, Ar^1 = 4-Cl-C_6H_4; i)R = Ar = $Ar^1 = C_6H_5$; j)R = C_6H_5, Ar = C_6H_5, Ar^1 = 4-Cl-C_6H_4; k)R = C_6H_5, Ar = 4-Me-C_6H_4, $Ar^1 = C_6H_5$; l) R = C_6H_5, Ar = 4-Me-C_6H_4, Ar^1 = 4-Cl-C_6H_4; m) R = C_6H_5,Ar = 4-Br-C_6H_4, $Ar^1 = C_6H_5$; n)R = C_6H_5, Ar = 4-Br-C_6H_4, Ar^1 = 4-Cl-C_6H_4; o)R = C_6H_5, Ar = 4-NO_2-C_6H_4, $Ar^1 = C_6H_5$; p)R = C_6H_5,Ar = 4-NO_2-C_6H_4, Ar^1 = 4-Cl-C_6H_4

Table 1
Comparison of Two Methods in Robinson Annulation

			Stirred in K_2CO_3[23]		Stirred in [bmim]Br	
Cmpd	mp(°C)	*lit.* mp.[23]	Time (min)	Yield (%)	Time (min)	Yield (%)
3a	109–111	111–112[24]	60	85	35	95
3b	90–91	90–91[23]	40	80	30	90
3c	141–143	139–142[24]	50	85	35	95
3d	115–117	115–117[23]	60	80	30	90
3e	153–155	153–155[23]	30	80	20	90
3f	111–113	110–112[23]	30	82	15	90
3g	107–109	105–107[24]	20	60	15	85
3h	134–136	134–136[23]	20	60	10	90

Table 2
Comparison of two Procedures in the Preparation of Indazoles

Cmpd	mp(°C)	*lit.* mp.[25]	Acetic Acid[a,25] Yield (%)	[bmim]Br[b] Yield (%)
5a	215–216	215–217	77	85
5b	123–125	123–125	72	80
5c	159–160	158–160	75	85
5d	120–122	120–121	72	83
5e	146–148	146–148	70	80
5f	141–143	141–143	71	78
5g	157–158	157–158	65	78
5h	167–168	167–168	66	80
5i	170–173	170–173	82	85
5j	166–167	167–168	70	78
5k	182–184	182–184	80	85
5l	186–188	186–188	75	83
5m	213–215	213–215	71	75
5n	167–168	167–168	72	78
5o	150–151	150–151	77	85
5p	160–161	161–162	75	83

a) 6 hours in Ref. 25; b) 3.5 hours.

One of the advantages of ionic liquids is their ability to function as a recyclable reaction medium. The catalyst [bmim]Br could be recovered and reused from the reaction medium easily by washing with ether and evaporating the solvent under vacuum.[26]

Experimental Section

Yields refer to isolated pure products. The products were characterized by comparison of their spectral (IR, ^{1}H NMR, ^{13}C NMR) and melting points with authentic samples. All of the reactions were carried out in a hood with strong ventilation. IR spectra were recorded on a Magna-550 IR spectrophotometer. Spectra of solids were carried out using KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were determined on a Bruker DPX-400 M Hz using [D_6]DMSO as solvent and TMS as internal standard.

Typical Procedure for the Robinson Annulation Reaction in [bmim]Br (3a–h)

A mixture of the chalcone (1mmol), ethyl acetoacetate (130 mg, 1 mmol) and [bmim]Br (153 mg, 0.7 mmol) was stirred at room temperature for the period of time required to complete the reaction (TLC). The reaction mixture was extracted with ether (3 × 10 mL) and separated from the ionic liquid phase. The residual ionic liquid may be reused in the next run if necessary after a 2 h heat treatment under vacuum. The ethereal layer was

evaporated under reduced pressure and the product was recrystallyzed from ethanol. The spectral data of all products were identical to those reported in a previous paper.[23]

Typical Procedure for the Preparation of Indazole Derivatives (5a–p) in [bmim]Br

A mixture of **3a-h** (1 mmol) and [bmim]Br (153 mg, 0.7 mmol) was added to hydrazine hydrate or phenylhydrazine (1.5 mmol). The mixture was refluxed for 3.5 h at 90°C. The reaction mixture was extracted with ether (3×10 mL) and the ionic liquid phase was separated. The residual ionic liquid may be reused in the next run if necessary after a 2 h heat treatment under vacuum. The ethereal layer was evaporated under reduced pressure and the product was recrystallyzed from ethanol. The spectral data of all products were identical to those reported in a previous paper.[25]

Acknowledgements

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