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Multicomponent reactions in PEG-400: ruthenium-catalyzed synthesis of substituted pyrroles

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ABSTRACT

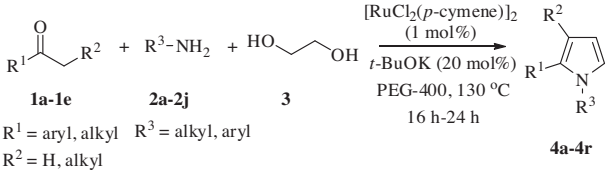
An efficient and eco-friendly method for the synthesis of substituted pyrroles has been developed via ruthenium-catalyzed multicomponent reaction of ketone, amine, and ethylene glycol in PEG-400 as solvent medium without using any external ligand. The catalytic system and solvent can be recycled with the same, as well as different, ketones with minimum loss of Ru-catalyst activity.

Multicomponent reactions (MCRs),[1] eco-friendly solvents,[2] and catalysis[3] have been central themes in green chemistry. Incorporation of these principles into the formation of new C–C and C–X bonds paves the way toward the preparation of new chemicals and products in agrochemicals, pharmaceuticals, and materials in an economical fashion. In particular, the use of recyclable and reusable solvents is gaining prominence in organic reactions.[4] In this direction, we have demonstrated in our early studies that PEG-400 is a preferred solvent medium wherein the expensive metals and their complex could be recovered and reused effectively without loss of activity.[5]

Since the first synthesis of 'pyrrole' ring by Knorr way back in 1884, the preparation of pyrroles has come a long way over the past century.[6] Several approaches viz., [3+2] cycloadditions,[7] [4+1] approach,[8] [2+2+1] approach,[9] and intramolecular versions[10] have been developed for the synthesis of pyrroles. These approaches are compiled in excellent reviews by Ferreira[11] and Menendez.[12] Recently, a novel three-component method for the pyrrole synthesis has been reported by Beller's group using ruthenium catalysis, assisted by xantphos as ligand, in a [2+2+1] strategy for the pyrrole formation.[13] This work combined with our experience in using PEG-400 as a solvent medium,[5] prompted us to look at the recyclability of expensive Ru-catalyst in such a pyrrole synthesis.

The results pertaining to Ru-catalyzed three-component pyrrole synthesis with a recyclable medium (Ru and PEG-400) are reported herein (Scheme 1). Furthermore, a significant advantage of the described method is that the expensive ligand (xantphos) is avoided since the PEG-400 acts as external ligand.[14]

In the first instance, cyclopentanone **1a**, cyclohexylamine **2a**, and ethylene glycol **3** were chosen as partners in the [2+2+1] condensation process (Table 1, entry 1). The reaction in PEG-400 in the presence of 1 mol % $[RuCl_2(p\text{-cymene})]_2$ and 20 mol % *t*-BuOK catalytic system was successful and 1,2,3-trisubstituted pyrrole **4a** was isolated in 75% yield, after a routine work-up process.[5k,15] With this observation on hand, the reaction generality was studied by performing experiments with various substrates. Keeping cyclopentanone **1a** and ethylene glycol **3** as the common partners, 4-methoxybenzylamine **2b** (Table 1, entry 2) and *n*-butyl amine **2c** (Table 1, entry 3) as variable amine counterparts, pyrroles **4b**, **4c** were obtained in decent yields. To understand the patterns for aryl ketones, phenylethylketone **1b** and ethylene glycol **3** as



Scheme 1. Synthesis of substituted pyrroles in PEG-400.

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0040-4039/

Table 1
Ruthenium-catalyzed synthesis of substituted pyrroles

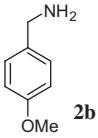
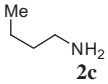
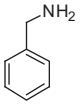
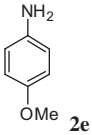
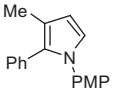
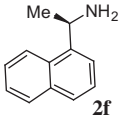
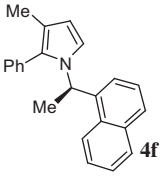
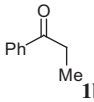
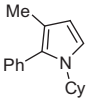
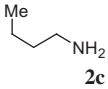
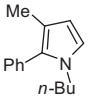
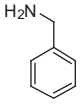
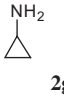
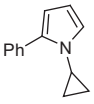
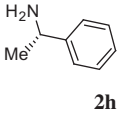
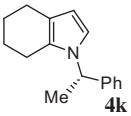
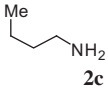
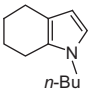
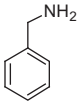
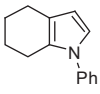
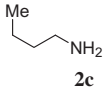
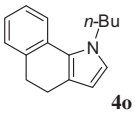
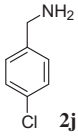
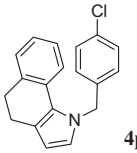
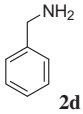
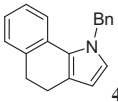
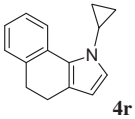
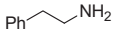
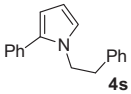
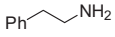
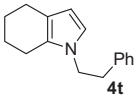
Entry	Ketone	Amine	Product[a]	Time (h)	Yield[b] (%)
1	 **1a**	 **2a**	 **4a**	16	75
2	 **1a**	 **2b**	 **4b**	20	74
3	 **1a**	 **2c**	 **4c**	16	70
4	 **1b**	 **2d**	 **4d**	16	85
5	 **1b**	 **2e**	 **4e**	24	70
6	 **1b**	 **2f**	 **4f**	20	85
7	 **1b**	 **2a**	 **4g**	20	65
8	 **1b**	 **2c**	 **4h**	16	75
9	 **1c**	 **2d**	 **4i**	24	75
10	 **1c**	 **2g**	 **4j**	24	70
11	 **1d**	 **2h**	 **4k**	16	80
12	 **1d**	 **2c**	 **4l**	16	75
13	 **1d**	 **2d**	 **4m**	16	75

Table 1 (*continued*)

Entry	Ketone	Amine	Product[a]	Time (h)	Yield[b] (%)
14	 **1d**	 **2i**	 **4n**	20	70
15	 **1e**	 **2c**	 **4o**	16	80
16	 **1e**	 **2j**	 **4p**	16	82
17	 **1e**	 **2d**	 **4q**	16	85
18	 **1e**	 **2g**	 **4r**	20	75
19	 **1c**	 **2k**	 **4s**	16	54 (60)[c]
20	 **1d**	 **2k**	 **4t**	16	75 (82)[c]

[a] All products were characterized by ^{1}H, ^{13}C NMR, and mass spectroscopy.
[b] Isolated yield after column chromatography.
[c] Reported yield Ref. 13a.

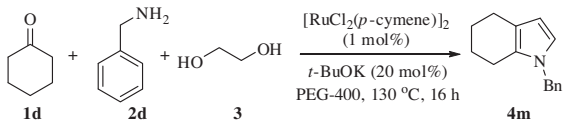
common partners were treated with benzylamine **2d**, 4-methoxy aniline **2e**, (*R*)-(+)-1-(1-naphthyl)ethyl amine **2f**, cyclohexylamine **2a**, and *n*-butyl amine **2c** to give the trisubstituted pyrroles **4d**–**h**, respectively, in satisfactory yields (Table 1, entries 4–8). In addition, other ketones such as acetophenone **1c** with benzylamine **2d** and cyclopropylamine **2g** gave disubstituted pyrroles **4i** and **4j**, respectively, in acceptable yields (Table 1, entries 9 and 10). The cyclohexanone **1d** provided bicyclic fused pyrroles **4k**–**n** with (*S*)-phenylethylamine **2h**, butylamine **2c**, benzylamine **2d**, and aniline **2i** consistently well (Table 1, entries 11–14). Another ketone, α-tetralone **1e** was attempted with butylamine **2c**, 4-chlorobenzylamine **2j**, benzylamine **2d**, and cyclopropylamine **2g** providing angular tricyclic pyrroles **4o**–**r**, respectively, in the 75–85% yield range (Table 1, entries 15–18). For direct comparison of present method with Beller's protocol, the experiments were performed with 2-phenylethylamine (**2k**) as one of the partners (Table 1, entries 19 and 20). The observations reveal that the yields obtained with the new system are marginally lower, however offers an additional advantage that the external ligand is not required.

Further, the efficacy of the developed method by recycle and reuse[12] of expensive ruthenium catalyst, has been demonstrated. Toward this, entry 13 (Table 1) has been chosen as representative example. Thus, **1d** and **2d** were condensed with ethylene glycol **3** in the presence of *t*-BuOK for over five times using the same PEG-400 and ruthenium catalyst with good yields without significant loss of catalytic activity (Table 2). Also, the cross over experiments performed with three different ketones (Table 3) demonstrated that the products could be completely extracted from PEG and no detectable contaminations were observed. However, due the aqueous work-up process, 20 mol % *t*-BuOK has to be added after each run. Here also, an addition of 0.2 mol % [$RuCl_2$(*p*-cymene)]$_2$ allowed us to improve the yields in next runs.

Based on these findings, it may be inferred that the [2+2+1] condensation for pyrrole synthesis proceeds smoothly in PEG, even in the absence of any added ligand, via imine formation between ketone and amine, followed by dehydrogenation of ethylene glycol to an in situ generated dialdehyde for further condensation to form pyrrole.[11]

Disappointingly, the substituted vicinal diols viz., 2,3-butanediol, 1,2-diphenylethane-1,2-diol, cyclohexane-1,2-diol, and 2-phenylethane-1,2-diol did not participate in the pyrrole synthesis. However, α-hydroxyacetone **5** when subjected to the

Table 2
Recyclability of catalyst in PEG-400



1d **2d** **3** **4m**

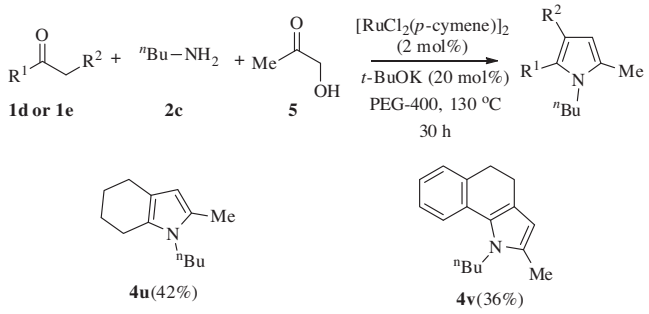
Run	1st	2nd	3rd	4th	5th
Yield[a] (%)	75	72	70	65 (70)*	63 (70)*

[a] Isolated yield after column chromatography.
* An additional 0.2 mol % 'Ru' catalyst was added to the reaction.

Table 3
Recyclability of catalyst and solvent in crossover experiments

Run	Ketone	Product	Yield[a] (%)
1st	**1d**	**4m**	75
2nd	**1e**	**4o**	70
3rd	**1b**	**4h**	65 (75)[*]

[a] Isolated yield after column chromatography.
[*] An additional 0.2 mol % 'Ru' catalyst was added to the reaction.



Scheme 2. Synthesis of α-methyl substituted pyrroles in PEG-400.

coupling protocol with ketones **1d** or **1e** and *n*-butylamine (Scheme 2) provided pyrroles **4u** and **4v** in moderate yields.

These results endorse that the developed methodology follows the major principles of green chemistry wherein catalyst and solvent are recyclable. This MCR is well tolerated in PEG-400, with H_2 and H_2O as byproducts, and additionally the molecules obtained, especially the tricyclic pyrroles, are potentially useful in bioorganic and medicinal chemistry.

In conclusion, we have successfully synthesized substituted pyrroles using readily accessible ketones, amines, and ethylene glycol using $[Ru(p\text{-cymene})Cl_2]_2$ as catalyst and potassium *tert*-butoxide as base in PEG-400 without using any extra ligand. In the process, the catalyst along with PEG solvent was recycled up to five times with the same ketone, as well as with different ketones.

Acknowledgments

This research has been performed as part of the Indo-French '*Joint Laboratory for Sustainable Chemistry at Interface*'. We thank CNRS, CSIR, University of Rennes 1, and CEFIPRA/IFCPAR for support of this research. V.P. and L.N.C thank CSIR, New Delhi, for research fellowship and R.C. thanks CSIR-SRA for financial assistance. SC thanks CSIR XII plan project ORIGIN (CSC-0108) for funding.

Supplementary data

Supplementary data (experimental and characterization data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.08.105.

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14. The OH groups of PEG can act as ligands see: (a) Mao, J.; Ji, S. J.; Guo, J.; Fang, F. *Tetrahedron* **2008**, *64*, 3905–3911; (b) Wang, Y.; She, J.; Jiang, Z. *Tetrahedron Lett.* **2009**, *50*, 593–596; (c) Reddy, G. C.; Balasubramanyam, P.; Salvanna, M.; Das, B. *Eur. J. Org. Chem.* **2012**, 471–474; (d) Framery, E.; Adidou, O.; Henry, C. G.; Safi, M.; Soufiaoui, M. *Tetrahedron Lett.* **2008**, *49*, 7217–7219; (e) Desouza, A. L. F.; Silva, A. C.; Antunes, O. A. C. *Appl. Organometal. Chem.* **2009**, *23*, 5–8; (f) Li, J. H.; Liu, W. J.; Xie, Y. X.; Liang, Y. *Synthesis* **2006**, *5*, 860–864; (g) Li, X.; Wu, Y.; Lu, C.; Shan, W. *Tetrahedron: Asymmetry* **2009**, *20*, 584–587.
15. *General experimental procedure:* To a stirred solution of ketone (1.0 mmol) in PEG-400 (4 mL) was added amine (1.5 mmol) at 25 °C in a glass pressure tube. After 5 min, diol (2.2 mmol) was added followed by $[Ru(p\text{-cymene})Cl_2]_2$ (0.01 mmol) and potassium *tert*-butoxide (0.2 mmol) successively. The pressure tube was tightly capped and heated to 130 °C. After completion of the reaction, it was cooled to room temperature. The solution was diluted with ether (10 mL), stirred for 10 min, and was allowed to stand in ice-salt bath to solidify PEG-400. The ether layer was decanted, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue obtained was purified by silica gel column chromatography using 1–5% ethyl acetate in petroleum ether as eluent to give pure products. The residual PEG–catalyst system was brought to room temperature and reused in next run/experiment.