

An improved solvent-free procedure for synthesis of bis(indolyl)methanes

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INTRODUCTION

Indoles and their derivatives are widely present in bioactive metabolites of compounds of both terrestrial and marine origin.¹ The bis(indolyl)methane (BIM) of simpler structure, bis(3-indolyl)methane, Figure 1, has recently been used as chemotherapy in cancer treatment.²

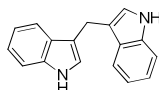


Figure 1. Bis(indolyl)methane.

Because of BIM's versatile biological activities, in particular the pharmacological one, various methods are mentioned for their preparation.³ A drawback of most of the described methods is the use of expensive and toxic reagents and volatile solvents. In this work, because of our interest in the development of new efficient and green methodologies, we decided to study the electrophilic substitution reaction of indoles with carbonyl compounds to obtain bis(indolyl)methanes using silica gel as recyclable catalyst.

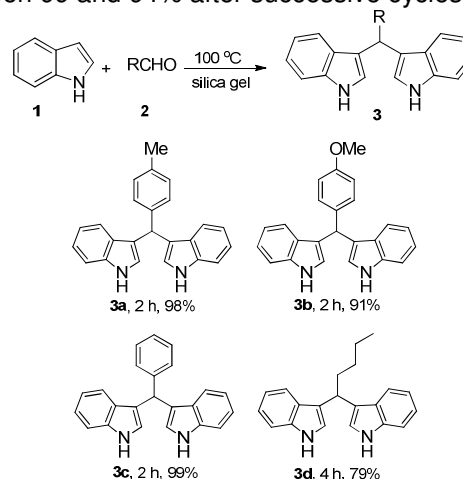
RESULTS AND DISCUSSION

Our initial studies have focused on the development of an optimum set of reaction conditions. Careful analysis revealed that the best conditions for the electrophilic substitution reaction was the use of silica gel (50 mg), indole (1.0 mmol) and aldehyde (0.6 mmol) at 100 °C under air atmosphere (Scheme 1).

Thus, the protocol was extended to other aromatic and aliphatic aldehydes. For aromatic aldehydes, the bis(indolyl)methanes **3** were obtained in excellent yields after stirring at 100 °C for 2 h. However, when we used aliphatic aldehyde, pentanal, the 3,3'-pentane-1,1-diylbis-1*H*-indole (**3d**) was obtained in 79% after 4 h of reaction.

The silica gel can be successfully reused up to ten times without any pre-treatment with excellent

results. Thus, for example, after the completion of the reaction of indole and benzaldehyde, the product **3c** was simply extracted with ethyl acetate (3 x 5 mL) and the silica gel was reused in a new electrophilic substitution after removing the AcOEt under vacuum. The product was obtained in yields between 99 and 94% after successive cycles



Scheme 1. Synthesis of bis(indolyl)methanes.

CONCLUSION

In summary, the silica gel has proved to be an effective and recyclable catalyst for the synthesis of bis(indolyl)methanes. The possibility of direct reuse of the silica for several cycles, together with the solvent-free conditions is particularly relevant considering the green chemistry concept.

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REFERENCES

- Sundberg, R. J. *Indoles*; Academic Press: San Diego, 1996.
- Safe, S.; Papineni, S.; Chintharlapalli, S. *Cancer Lett.* **2008**, 269, 326.
- Nagarajan R.; Perumal, P. T. *Tetrahedron* **2002**, 58, 1229; Chakrabarty, M.; Ghosh, N.; Basak, R.; Harigaya, Y. *Tetrahedron Lett.* **2002**, 43, 4075; Chen, D.; Yu, L.; Wang, P. G. *Tetrahedron Lett.* **1996**, 37, 4467; Deb, M. L.; Bhuyan, P. J. *Synlett* **2008**, 325; Shiri, M.; Zolfigol, M. A.; Kruger, H. G.; Tanbakouchian, Z. *Chem. Rev.* **2010**, 110, 2250.