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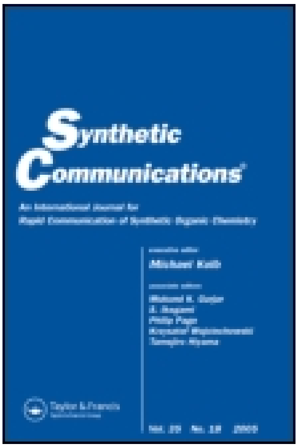

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Molecular Iodine: An Efficient and Environment Friendly Catalyst for the Synthesis of 3,5-Bis-(arylmethylidene)-tetrahydropyran-4-ones

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MOLECULAR IODINE: AN EFFICIENT AND ENVIRONMENT FRIENDLY CATALYST FOR THE SYNTHESIS OF 3,5-*BIS*-(ARYLMETHYLIDENE)-TETRAHYDROPYRAN-4-ONES

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A rapid, efficient, convenient and cost-effective procedure has been developed for the synthesis of 3,5-*bis*-(arylmethylidene)-tetrahydropyran-4-ones by the condensation of tetrahydropyran-4-one with araldehydes in the presence of catalytic amount of iodine to obtain the products in good to excellent yield. The reactions work at 25°C and go to completion within 30–60 min.

Keywords: Araldehydes; 3,5-*bis*-(arylmethylidene)-tetrahydropyran-4-ones; iodine; tetrahydropyran-4-one

INTRODUCTION

3,5-*Bis*-(arylmethylidene)-tetrahydropyran-4-ones are very important group of heterocycles that have many applications in both pharmaceutical and industrial research. They are also used widely in bioorganic applications,[1] and as useful and key precursors in the synthesis of a number of heterocyclic compounds.[2] On the other hand, only a few methods are available in the literature for the synthesis of these bioactive molecules. The important methods include the reaction of tetrahydropyran-4-one or tetrahydrothiopyran-4-one with substituted benzaldehydes in the presence of catalysts such as $Ba(OH)_2$ in MeOH,[3] a mixture of $MgBr_2 \cdot OEt_2$ and Et_3N in MeOH,[4] $LiClO_4$-$TMSNEt_2$,[5] HCl in AcOH,[6] and a mixture of LiBr-Et_3N in CH_2Cl_2.[7] However, many of these methods suffer drawbacks such as: i) Low yield of the products; ii) Require additional reagent; and iii) Take long duration for completion of the reaction.

Molecular iodine has also received considerable attention in organic synthesis as an inexpensive, easily available and environmentally benign catalyst for effecting various organic transformations.[8] In continuation of our research program on effective utilization of simple and readily available reagents for various organic

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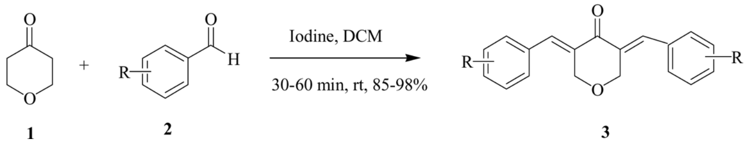


Scheme 1. 3,5-*Bis*-(arylmethylidene)-tetrahydropyran-4-ones synthesis from araldehydes and tetrahydropyran-4-one.

transformations and for the synthesis of biologically important compounds. We in this paper, describe our finding on the formation of 3,5-*bis*-(arylmethylidene)-tetrahydropyran-4-ones via a double condensation reaction of araldehydes with tetrahydropyran-4-one in the presence of catalytic amount of Iodine at room temperature to get good to excellent yield of the desired products (**3**, Scheme 1).

Recently, we from our laboratory, have reported procedures wherein molecular iodine has been utilized as an efficient catalyst for the synthesis of azalactones,[9a] β-acetamido-β-aryl-propiophenones[9b] and xanthenes.[9c]

RESULTS AND DISCUSSION

As a preliminary study, we treated *p*-anisaldehyde (10 mmol) with tetrahydropyran-4-one (5 mmol) and catalytic iodine to get 3,5-*bis*-(4-methoxybenzylidene)-tetrahydropyran-4-one in DCM. To optimize the amount of iodine required for the catalytic activity 2 mmol, 1 mmol, 0.5 mmol and 0.1 mmol of iodine was employed for the purpose, and the best result was obtained with 0.1 mmol of iodine in terms of yield and reaction duration at 25 °C (95%, 60 min).

In the absence of iodine, the reaction did not proceed. We next investigated the scope and generality of the reaction in which 3,5-*bis*-(arylmethylidene)-tetrahydropyran-4-ones (**3a**–**3h**, Table 1) were successfully prepared in high yield using various substituted araldehydes. In all cases, the reactions proceed rapidly and go to completion within 30–60 min at 25 °C.

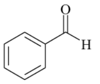
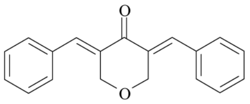
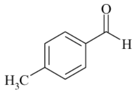
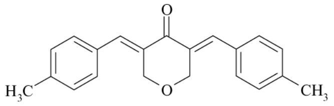
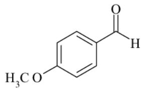
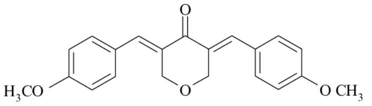
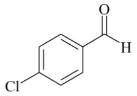
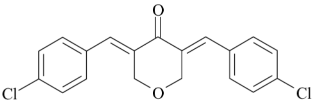
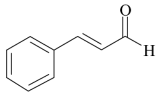
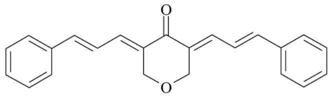
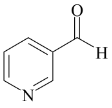
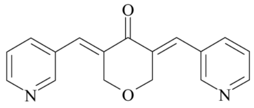
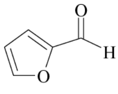
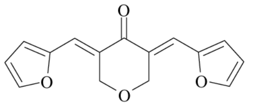
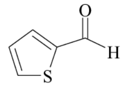
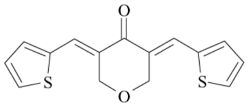
MECHANISM

A plausible mechanism for the formation of 3,5-*bis*-(arylmethylidene)-tetrahydropyran-4-ones has been envisaged in Scheme 2. It is assumed that, araldehyde gets activated in the presence of iodine in the first step of the reaction. In the subsequent step condensation of the activated araldehyde with tetrahydropyran-4-one [which may exist in the enolic form] takes place to give **6**, followed by elimination of a molecule of water to give the monoarylmethylidene intermediate **7** (not isolated). **7** may react with another molecule of activate araldehyde in the next step to give the product **3** as shown in Scheme 2.

EXPERIMENTAL

All reagents were commercial and used without further purification. The products were characterized by IR, ^{1}H NMR, ^{13}C NMR, and LC-MS spectral analyses. The IR and NMR spectra of the products were recorded on Shimadzu FT-IR-8400s

Table 1. Synthesis of 3,5-*bis*-(arylmethylidene)-tetrahydropyran-4-ones from tetrahydropyran-4-one and araldehydes

Entry	Aldehyde (**1**)	Product (**3**)[a]	Time (min)	Yield (%)[b]	Mp (°C)/lit.[5]
3a			30	98	186/185–187
3b			50	90	109–110/110
3c			60	95	180/175–177
3d			55	85	169/168–170
3e			60	92	205/206–208
3f			50	93	190/192–194
3g			55	93	173/170–172
3h			60	89	196/195–197

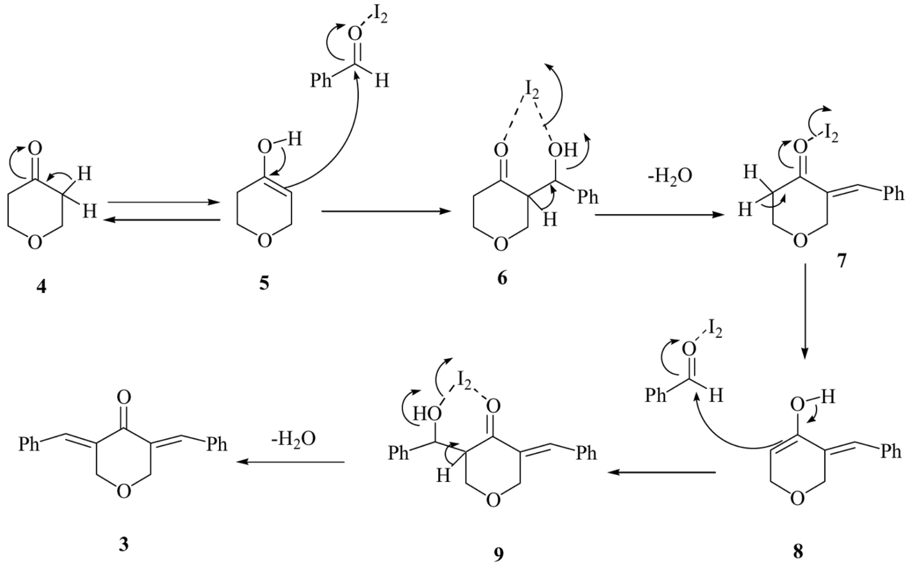
[a] All the products are known and are characterized by IR (entries **3a**–**3h**), ^{1}HNMR (entries **3a**–**3d** and **3g**), LC-mass (entries **3a**–**3d**) spectral analysis from Mp's (entries **3a**–**3h**) and comparison with the samples prepared by reported method [Ref 5].

[b] Isolated yields.

and Bruker AMX 200-MHz spectrophotometers respectively. LC-MS was performed on an Agilent Technologies 1200 series instrument.

Typical Procedure for the Preparation of 3,5-*Bis*-(arylmethylidene)-tetrahydropyran-4-ones

A mixture of tetrhydrpyran-4-one (**1**, 5 mmol), araldehyde (**2**, 10 mmol) in DCM (20 ml) was stirred at 25 °C in the presence of iodine (0.1 mmol) for an



Scheme 2. A plausible mechanism for the formation of 3,5-*bis*-(arylmethylidene)-tetrahydropyran-4-ones.

appropriate time (Table 1). The course of the reaction was monitored by TLC (15% ethyl acetate in light petrol). At the end of the reaction, a syrupy liquid was obtained which when allowed to stand at room temperature for 30 min gave a solid. The solid so obtained was washed with saturated $Na_2S_2O_3$ solution and dried over anhydrous $MgSO_4$ to get the crude product. The crude was subjected to purification by recrystallization from ethyl acetate.

CONCLUSION

In conclusion a rapid, efficient and cost-effective procedure has been developed for the synthesis of 3,5-*bis*-(arylmethylidene)-tetrahydropyran-4-ones. The procedure is simpler and faster than the protocols published to date. It is also consistent with a green chemistry approach since no heating or additional equipment is required. The catalyst used is inexpensive, non-toxic, non-corrosive and readily available chemical that is commonly found in most organic chemistry laboratories. The simplicity, together with the use of inexpensive, non-toxic and environmentally benign catalyst-Iodine at 25 °C is a remarkable feature of the procedure.

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REFERENCES

1. (a) Deli, J.; Lorand, T.; Szabo, D.; Foldesi, A. Potential bio-active pyrimidine Derivatives 1: 2-Amino-4-aryl-8-arylidene-3,4,5,6,7,8-hexahydrochinazolines. *Pharmazie* **1984**, *39*, 539–540; (b) Guilford, W. J.; Shaw, K. J.; Dallas, J. L.; Koovakkat, S.; Lee, W.; Liang, A.; Light, D. R.; McCarrick, M. A.; Whitlow, M.; Ye, B.; Morrissey, M. M. Synthesis, characterization, and structure–activity relationships of amidine-substituted (*bis*)benzylidene-cycloketone olefin isomers Novel Bisarylmethylidenes of Cyclic Enones as potent and selective factor Xa inhibitors. *J. Med. Chem.* **1999**, *42*, 5415–5425; (c) Artico, M.; Di Santo, R.; Costi, R.; Novellino, E.; Greco, G.; Massa, S.; Tramintano, E.; Marongiu, M. E.; De Montis, A.; La Colla, P. Geometrically and conformationally restrained cinnamoyl compounds as inhibitors of *HIV*-1 integrase: Synthesis, biological evaluation, and molecular modeling. *J. Med. Chem.* **1998**, *41*, 3948–3960; (d) Jia, Z. C.; Quail, J. W.; Arora, V. K.; Dimmock, J. R. Structure of 3,5-*bis*(benzylidene)-1-methyl-4-piperidone methobromide hemithanol solvate. *Acta Cryst., Sect. C.* **1989**, *45*, 1117–1118; (e) Gangadhara, K. K. Synthesis and characterization of photo-cross-linkable main-chain liquid-crystalline polymers containing *bis*(benzylidene)cycloalkanone units. *Polymer* **1995**, *36*, 1903–1910.
2. (a) Ward, D. E.; Nixey, T. E.; Gai, Y.; Hrapchak, M. J.; Abaee, M. S. Intramolecular Diels–Alder reactions of 2*H*-thiopyran dienes. *Can. J. Chem.* **1996**, *74*, 1418–1436; (b) Ward, D. E.; Abaee, M. S. Intramolecular Diels−Alder Reaction by Self-Assembly of the Components on a Lewis Acid Template. *Org. Lett.* **2000**, *2*, 3937–3940; (c) Ward, D. E.; Sales, M.; Chuk, C. M.; Jianheng, S.; Pradip, K. S.; Cheng, G. Influence of the β-Alkoxy Group on the Diastereoselectivity of Aldol Reactions of Tetrahydro-4*H*-thiopyran-4-one with 4-Alkoxytetrahydro-2*H*-thiopyran-3-carboxaldehydes. *J. Org. Chem.* **2001**, *67*, 1618–1629.
3. Mai, A.; Cheng, D.; Bedford, M. T.; Valente, S.; Nebbioso, A.; Perrone, A.; Brosch, G.; Sbardella, G.; De Bellis, F.; Miceli, M.; Altucci, L. Epigenetic multiple ligands: Mixed histone/protein methyltransferase, acetyltransferase, and class III deacetylase (sirtuin) inhibitors. *J. Med. Chem.* **2008**, *51*(7), 2279–2290.
4. Abaee, M. S.; Mojtahedi, M. M.; Zahedi, M. M.; Sharifi, R. A highly efficient method for solvent-free synthesis of bisarylmethylidenes of pyranones and thiopyranones. *Heteroatom Chem.* **2007**, *18*(1), 44–49.
5. Abaee, M. S.; Mojtahedi, M. M.; Zahedi, M. M.; Bolourtchian, S. M. First highly efficient synthesis of *bis*(arylmethylidene)pyranones mediated by lithium perchlorate. *Synth. Commun.* **2006**, *36*(2), 199–206.
6. Costi, R.; Santo, R. D.; Artico, M.; Massa, S.; Ragno, R.; Loddo, R.; La Colla, M.; Tramontano, E.; La Colla, P.; Pani, A. 2,6-*Bis*(3,4,5-trihydroxybenzylydene) derivatives of cyclohexanone-novel potent *HIV*-1 integrase inhibitors that prevent *HIV*-1 multiplication in cell-based assays. *Bioorg. Med. Chem. Lett.* **2004**, *12*(1), 199–215.
7. Abaee, M. S.; Mojtahedi, M. M.; Zahedi, M. M.; Mesbah, A. W.; Ghandchi, N. M.; Massa, W. *Phosphorus, Sulfur, Silicon.* **2007**, *182*, 2891–2895.
8. (a) Banik, B. K.; Fernandez, M.; Alvarez, C. Iodine-catalyzed highly efficient Michael reaction of indoles under solvent-free condition. *Tetrahedron Lett.* **2005**, *46*, 2479–2482; (b) Hessian, K. O.; Flynn, B. L. Iodine-induced reaction cascades for the rapid construction of variously substituted benzothiophenes. *Org. Lett.* **2003**, *5*, 4377–4380.
9. (a) Madhusudana Reddy, M. B.; Pasha, M. A. Molecular iodine catalyzed mild, effective and eco-friendly microwave assisted one-pot synthesis of 5-arylmethylidene-2-phenyloxazol-4-ones (azalactones) under solvent-free condition. *Synth. Commun.* **2009** (LSYC-2009-2879, In press); (b) Pasha, M. A.; Jayashankara, V. P.; Swamy, N. R. A

simple and efficient procedure for the one pot synthesis of β-acetamido-β-aryl-propiophenones by molecular iodine catalyzed Tandem reaction. *Synth. Commun.* **2007**, *37*, 1551–1556; (c) Pasha, M. A.; Jayashankara, V. P. Molecular iodine catalyzed synthesis of aryl-14*H*-dibenzo[*a,j*]xanthenes under solvent free condition. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 621–623.