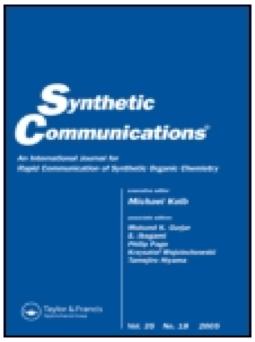


Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

Practical Synthesis of Diaryloxymethanes

Wenming Liu , Joanna Szewczyk , Liladhar Waykole , Oljan Repic & Thomas J. Blacklock

To cite this article: Wenming Liu , Joanna Szewczyk , Liladhar Waykole , Oljan Repic & Thomas J. Blacklock (2003) Practical Synthesis of Diaryloxymethanes, Synthetic Communications, 33:10, 1751-1754, DOI: 10.1081/SCC-120018936

To link to this article: http://dx.doi.org/10.1081/SCC-120018936

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 10, pp. 1751–1754, 2003

Practical Synthesis of Diaryloxymethanes

Wenming Liu, Joanna Szewczyk, Liladhar Waykole,*
Oljan Repic, and Thomas J. Blacklock

Process R & D, Chemical and Analytical Development,
Novartis Institute for Biomedical Research,
East Hanover, New Jersey, USA

ABSTRACT

Diaryloxymethanes were prepared by treating phenols with sodium hydride and dichloromethane in *N*-methyl-pyrrolidinone (NMP) at 40°C.

Key Words: Diaryloxymethane; Phenol; Sodium hydride; Methylene chloride; *N*-methyl-pyrrolidinone.

---

*Correspondence: Liladhar Waykole, Process R & D, Chemical and Analytical Development, Novartis Institute for Biomedical Research, One Health Plaza, East Hanover, NJ 07936, USA; Fax: 973-781-2188; E-mail: liladhar.waykole@pharma.novartis.com.

DOI: 10.1081/SCC-120018936 0039-7911 (Print); 1532-2432 (Online)

www.dekker.com

INTRODUCTION

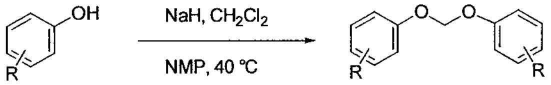
Diaryloxymethanes have been used in various areas, most recently as fungicides.[1] Usually they were prepared by the methylenation of appropriate phenol with diiodomethane,[2] bromochloromethane,[3] and dichloromethane.[4] Different inorganic bases, such as K_2CO_3,[4] Cs_2CO_3,[3] NaH,[5] and several polar solvents, such as dimethylsulfoxide (DMSO) and dimethylformamide (DMF) have been used to facilitate the conversion. Often the use of a sealed tube is required due to the volatility of the methylenating agents.[3] Use of dibenzo 18-crown-6 ether[6] and biphasic phase transfer catalysis conditions using quaternary ammonium salts[7] are also reported albeit requiring longer reaction times.

Recently, catalyst[8] and polymer-supported reagent[9] have shown to expedite the desired methylenation. Dichloromethane is particularly of interest because it is the cheapest among these methylenation agents. However, the use of dichloromethane to achieve the methylenation requires higher reaction temperatures (up to 120°C).[4] In the course of our project, we encountered a task of preparing high purity diaryloxymethane at low temperature. In this article, we report a method for the synthesis of diaryloxymethanes from various phenols and dichloromethane in the presence of sodium hydride in *N*-methylpyrrolidinone (NMP).

RESULTS AND DISCUSSION

We judiciously selected to use dichloromethane and sodium hydride over other reagents because of their low cost. The choice of NMP over DMSO and DMF was due to the safety concern during scale-up.[10] The results are summarized in the following table. In general, phenol (3 mmol) was dissolved in 4 mL of NMP, and then the solution was cooled to 0°C. Solid sodium hydride (3.3 mmol) was added in portions followed by the addition of 0.5 mL of dichloromethane. The reaction mixture was slowly warmed up to 40°C. After the complete consumption of the phenol was confirmed by HPLC, the reaction mixture was quenched with water and partitioned between ethyl acetate and water. The organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solution was concentrated, and the residue was passed through a silica gel column. Evaporation of the collected eluent (5% EtOAc/heptane) gave the product with greater than 98% purity (Sch. 1).

With the exception of *o*-nitrophenol, other phenols were converted to their corresponding diaryloxymethanes in excellent yields (92–99%).



Scheme 1.

Table 1. Synthesis of diaryloxymethanes.

Entry	*R*	Time (h)	Yield[a] (%)
1	H	24	97
2	*m*-Cl	20	97
3	*p*-Cl	9	98
4	*m*-Me	7	93
5	*p*-Me	4	92
6	*m*-MeO	4	98
7	*p*-MeO	2	99
8	*o*-NO_2	18	0

[a] All yields refer to isolated products, fully characterized by spectral data.

The reaction time showed strong dependence on the substituent and its position on the phenyl ring. An electron-donating group on the phenyl ring enhances the nucleophilicity of the phenoxide and therefore shortens the reaction time. The effect is more pronounced when the group is at the para-position (Table 1, Entries 3, 5, and 7).

In summary, we have developed a method to prepare diaryloxymethane through the methylenation of phenol using dichloromethane and sodium hydride in *N*-methyl-pyrrolidinone.

REFERENCES

1. Arnoldi, A.; Carzaniga, R.; Morini, G.; Merlini, L.; Farina, G. J. Agric. Food. Chem. **2000**, *48*, 2547–2555.
2. Miron, S.; Lowy, A. J. Am. Chem. Soc. **1951**, *73*, 1872–1873.
3. Roman, E.; Peinador, C.; Mendoza, S.; Kaifer, A.E. J. Org. Chem. **1999**, *64*, 2577–2578.
4. Fujita, M.; Yamashite, M. Nippon Kagaku Kaishi **1975**, *2*, 331–333.
5. Delogu, G.; Fabbri, D.; Dettori, M.A. Tetrahedron: Asymmetry **1998**, *9*, 2819–2826.

6. Reuter, C.; Wienand, W.; Hubner, G.M.; Seel, C.; Vogtle, F. Chem. Eur. J. **1999**, *5*, 2692.
7. (a) Taniguchi, H.; Nomura, E. Chem. Lett. **1988**, 1773; (b) Dehmlow, E.V.; Schmidt, J. Tetrahedron Lett. **1976**, *2*, 95.
8. (a) Taniguchi, H.; Otsuji, Y.; Nomura, E. Bull. Chem. Soc. Jpn. **1995**, *68*, 3563–3567; (b) Hopf, H.; Utermohlen, R.; Jones, P.G.; Desvergne, J.-P.; Bouas-Laurent, H. J. Org. Chem. **1992**, *57*, 5509–5517.
9. Salunkhe, M.M.; Salunkhe, D.G.; Kanade, A.S.; Mane, R.B.; Wadgaonkar, P.P. Synth. Commun. **1990**, *20* (8), 1143–1147.
10. DeWall, G. Chem. & Eng. News **1982**, *Sept*. *13*, 5.

Received in the USA August 16, 2002