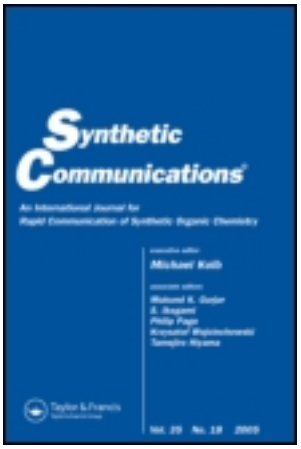

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Accepted author version posted online: 08 Nov 2013.Published online: 24 Feb 2014.

To cite this article: J. Mason Hoffman, Justin N. Miller, Margaret E. Gardner, Danielle R. LePar & Rongson Pongdee (2014) Synthesis of N,N-Diethylbenzamides via a Nonclassical Mitsunobu Reaction, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 44:7, 976-980, DOI: 10.1080/00397911.2013.839796

To link to this article: http://dx.doi.org/10.1080/00397911.2013.839796

Synthetic Communications®, 44: 976–980, 2014

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2013.839796

SYNTHESIS OF *N,N*-DIETHYLBENZAMIDES VIA A NONCLASSICAL MITSUNOBU REACTION

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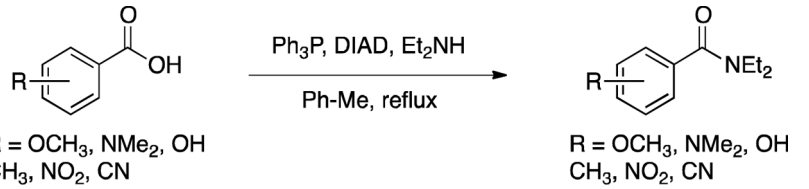
GRAPHICAL ABSTRACT



Abstract *The use of the Mitsunobu reaction for the synthesis of* N,N-*diethylbenzamides affords* ortho-, meta-, *and* para-*substituted benzamides containing both electron-donating and electron-withdrawing groups. While the preparation of numerous functional groups has been efficiently demonstrated employing the Mitsunobu reaction, our methodology represents the first application of the Mitsunobu reaction for the construction of benzamides using benzoic acid and amine starting materials. Moreover, this synthetic transformation is believed to proceed via a nonclassical mechanism involving the existence of an acyloxyphosphonium ion.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

Keywords Acylation; amides; Mitsunobu reaction

INTRODUCTION

The regioselective preparation of functionalized aromatic and heteroaromatic compounds remains an area of fundamental importance within the synthetic community. The presence of these architectural motifs in biologically active secondary metabolites and synthetic compounds of pharmaceutical value has continued to fuel the development of methodology for their efficient construction. One of the most

Received August 21, 2013.

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powerful synthetic transformations available for the regiocontrolled introduction of various functional groups onto aromatic scaffolds is the directed *ortho*-metalation (D*o*M) reaction, extensively studied by Snieckus and coworkers over the past 30 years.[1,2] Within this context, one of the most widely employed directing groups is the *N,N*-diethylamide functional group owing to its strong Lewis basicity, which allows for tight coordination with the Lewis acidic lithium cation of the alkyllithium base to direct deprotonation of an *ortho*-position on the aromatic ring.

During the course of our work toward the synthesis of members of the angucycline family of antitumor antibiotics, we envisioned employing a D*o*M strategy, utilizing a *N,N*-diethylamide directing group, for the preparation of a target fragment. Previously, our group disclosed the application of the Mitsunobu reaction for the efficient construction of arylbenzoates involving benzoic acids and phenols.[3] Within that context, we also postulated that our methodology proceeded through a nonclassical mechanism, involving an acyloxyphosphonium ion rather than the more traditional alkoxyphosphonium ion, that would allow for the introduction of various nucleophiles other than substituted phenols within a similar framework.[4] As such, we elected to explore the feasibility of preparing *N,N*-diethylbenzamides as an extension of our Mitsunobu methodology.

RESULTS AND DISCUSSION

Initially, we began investigating the conversion of 4-methoxybenzoic acid (**1**) to *N,N*-diethyl-4-methoxybenzamide (**2**), as depicted in Fig. 1. We explored various solvents, temperatures, and stoichiometric ratios in attempts to identify the optimal reaction conditions. We found that increasing the stoichiometry of DIAD, Ph_3P, and Et_2NH to more than 1.2 equivalents led to greater difficulty in obtaining pure products after column chromatography. In each case, we were pleased to obtain the desired benzamide product **2** following analysis of the ^1H NMR spectra. However, each sample was contaminated, presumably by the reduced azodicarboxylate and/or unreacted starting materials, from the Mitsunobu reaction. Over the years, numerous reports in the chemical literature have appeared, describing methods for the removal of by-products associated with the Mitsunobu reaction.[5] Unfortunately, our attempts to employ alternative azodicarboxylates, such as di-2-methoxyethyl azodicarboxylate (DMEAD), di-*p*-chlorobenzyl azodicarboxylate (DCAD), di-*tert*-butyl azodicarboxylate (DTBD), or structurally modified phosphines proved unsuccessful in alleviating our purification difficulties.[5d,5i,5k] After several attempts at varying the reaction conditions, we were pleased to discover that the inclusion of an acid–base extraction, involving 1 M sodium hydroxide, as part of the reaction workup afforded chromatographically pure benzamide **2** in good yield.

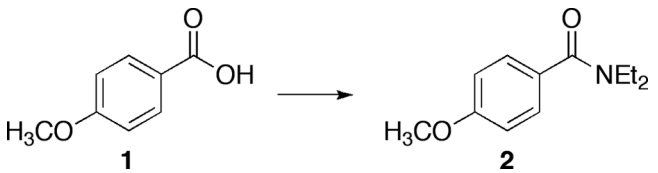
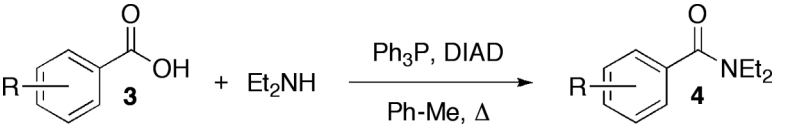
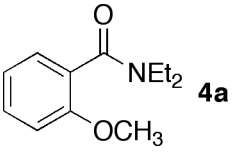
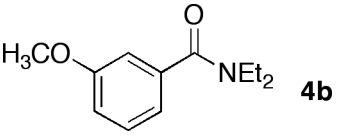
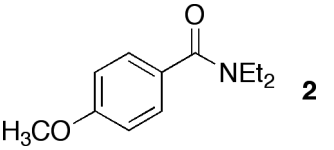
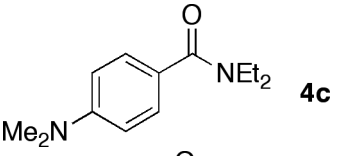
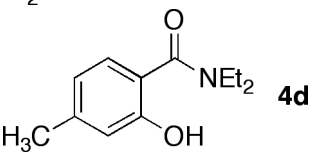
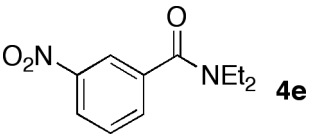
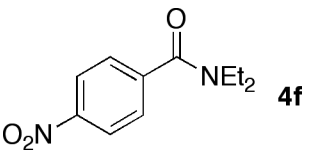
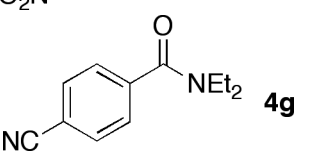


Figure 1.

Table 1. Synthesis of *N,N*-diethylbenzamides using the Mitsunobu reaction



Entry	Benzoic Acid	Product[a]	Yield (%)
1	**3a**, R = 2-OCH_3	 **4a**	64
2	**3b**, R = 3-OCH_3	 **4b**	52
3	**1**, R = 4-OCH_3	 **2**	67
4	**3c**, R = 4-$N(Me)_2$	 **4c**	64
5	**3d**, R = 2-OH, 4-CH_3	 **4d**	57
6	**3e**, R = 3-NO_2	 **4e**	35
7	**3f**, R = 4-NO_2	 **4f**	33
8	**3g**, R = 4-CN	 **4g**	26

[a]Products obtained were >95% pure by ^1H and ^{13}C NMR.

Next, we turned our attention to an examination of the substrate scope for our newfound methodology. As illustrated in Table 1, the reaction works reasonably well with electron-rich benzoic acids in the *ortho-, meta-*, or *para*-positions (entries 1–5). Additionally, free phenols (entry 5) can be employed with little detriment to the overall reaction outcome. It is worth mentioning that the preparation of benzamide **4d** via the acid chloride resulted in dramatically lower yields (41% compared to 57% employing our Mitsunobu methodology). To a lesser extent, the reaction is also tolerant of electron-poor benzoic acid substrates (entries 6–8). We believe that a partial reason for lower yields associated with electron-poor benzoic acids is incomplete consumption of the starting material employing our typical reaction conditions.

In summary, we have demonstrated a new application for the Mitsunobu reaction involving the preparation of *N,N*-diethylbenzamides. We believe that our methodology will benefit researchers employing directed *ortho*-metalation (D*o*M) strategies for a variety of synthetic applications. Additionally, our methodology may also be advantageous when traditional carboxylic acid derivative chemistry proves ineffective. Mechanistic studies of our nonclassical Mitsunobu reaction are currently under way and will be reported in due course.

EXPERIMENTAL

Triphenylphosphine (1.20 eq), diethylamine (1.20 eq), and the benzoic acid (1.00 eq) were dissolved in toluene (0.2 M solution) at room temperature and allowed to stir for 10 min. Diisopropylazodicarboxylate (1.20 eq) was then added dropwise and the reaction was heated to reflux overnight (18 h), at which time the reaction was diluted with EtOAc and washed with 1 M NaOH brine. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated in vacuo, and the resulting residue was purified by flash column chromatography (EtOAc/hexanes 2:1) to afford the desired benzamides.

ACKNOWLEDGMENTS

We gratefully acknowledge financial support from the National Institute of Allergy and Infectious Diseases (R15, AI084075-02) and the donors of the American Chemical Society Petroleum Research Fund (PRF 52168-UR1). Additionally, we thank the National Science Foundation, as part of its Major Research Instrumentation (MRI) Program (CHE-1126231), for the acquisition of a JEOL ECS-400 nuclear magnetic resonance spectrometer. Accurate mass measurements were performed by Dr. William Boggess of the Mass Spectrometry and Proteomics Facility at the University of Notre Dame.

SUPPORTING INFORMATION

Full experimental details, along with full characterization data for compounds **2** and **4a–g**, can be found via the Supplementary Content section of this article's Web page.

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