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Synthesis of *N,N*-Diethylbenzamides via a Non-Classical Mitsunobu Reaction

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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 non-classical mechanism involving the existence of an acyloxyphosphonium ion.

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 powerful synthetic transformations available for the regiocontrolled introduction of various functional groups onto aromatic scaffolds is the directed *ortho*-metalation (DoM) 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

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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 webpage.

allowing 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 towards the synthesis of members of the angucycline family of antitumor antibiotics, we envisioned employing a DoM 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 non-classical 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 Figure 1. We explored various solvents, temperatures, and stoichiometric ratios in attempts to identify the optimal reaction conditions.⁵ 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 material, 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.⁶ Unfortunately, our attempts to employ alternative azodicarboxylates such as di-2-methoxyethyl azodicarboxylate (DMEAD), di-*p*-chlorobenzyl azodicarboxylate (DCAD), or di-*tert*-butyl azodicarboxylate (DTBD) or structurally-modified phosphines proved unsuccessful in alleviating our purification difficulties.^{6d,6i,6k} 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 work-up afforded chromatographically pure benzamide **2** in good yield.

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.⁷ To a lesser extent, the reaction is also tolerant of electron-poor benzoic acid substrates (entries 6-8).⁸

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 (DoM) 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 non-classical Mitsunobu reaction are currently underway and will be reported in due course.

Experimental

General Procedure for the Synthesis of *N,N*-Diethylbenzamides

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 hr) at which time the reaction was diluted with EtOAc, washed with 1 M NaOH and brine. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, concentrated *in vacuo*, and the resulting residue was purified by flash column chromatography (EtOAc/hexanes 2:1) to afford the desired benzamides.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Snieckus V. *Chem Rev.* 1990; 90:879–933.
2. Hartung, CG.; Snieckus, V. *Modern Arene Chemistry*. Astruc, D., editor. Wiley-VCH; Weinheim, Germany: 2002. p. 330
3. Fitzjarrald VP, Pongdee R. *Tetrahedron Lett.* 2007; 48:3553–3557.
4. (a) Grochowski E, Hilton BD, Kupper RJ, Michejda CJ. *J Am Chem Soc.* 1982; 104:6876–6877.(b) Adam W, Narita N, Nishizawa Y. *J Am Chem Soc.* 1984; 106:1843–1845.(c) Varasi M, Walker KAM, Maddox ML. *J Org Chem.* 1987; 52:4235–4238.(d) Hughes DL, Reamer RA, Bergan JJ, Grabowski EJJ. *J Am Chem Soc.* 1988; 110:6487–6491.(e) Crich D, Dyker H, Harris RJ. *J Org Chem.* 1989; 54:257–259.(f) Camp D, Jenkins ID. *J Org Chem.* 1989; 54:3045–3049.(g) Camp D, Jenkins ID. *J Org Chem.* 1989; 54:3049–3054.(h) Hughes DL, Reamer RA. *J Org Chem.* 1996; 61:2967–2971. [PubMed: 11667155] (i) Harvey PJ, von Itzstein M, Jenkins ID. *Tetrahedron.* 1997; 53:3933–3942.(j) McNulty J, Capretta A, Laritchev V, Dyck J, Robertson AJ. *Angew Chem Int Ed.* 2003; 42:4051–4054.(k) Ahn C, Correia R, DeShong P. *J Org Chem.* 2002; 67:1751–1753. [PubMed: 11895388] (l) Dinsmore CJ, Mercer SP. *Org Lett.* 2004; 6:2885–2888. [PubMed: 15330639] (m) Schenk S, Weston J, Anders E. *J Am Chem Soc.* 2005; 127:12566–12576. [PubMed: 16144404]
5. We found that increasing the stoichiometry of DIAD, Ph₃P, and Et₂NH to more than 1.2 equivalents led to greater difficulty in obtaining pure products after column chromatography even with the inclusion of an acid-base extraction work-up protocol.
6. (a) Arnold LD, Assil HI, Vederas JC. *J Am Chem Soc.* 1989; 111:3973–3976.(b) Tunoori AR, Dutta D, Georg GI. *Tetrahedron Lett.* 1998; 39:8751–8754.(c) Kiankarimi M, Lowe R, McCarthy JR, Whitten JP. *Tetrahedron Lett.* 1999; 40:4497–4500.(d) Pelletier JC, Kincaid S. *Tetrahedron Lett.* 2000; 41:797–800.(e) Barrett AGM, Roberts RS, Schröder J. *Org Lett.* 2000; 2:2999–3001. [PubMed: 10986092] (f) Harned AM, He HS, Toy PH, Flynn DL, Hanson PR. *J Am Chem Soc.* 2004; 127:52–53. [PubMed: 15631444] (g) Véliz EA, Beal PA. *Tetrahedron Lett.* 2006; 47:3153–3156.(h) Proctor AJ, Beaument K, Clough JM, Knight DW, Li Y. *Tetrahedron Lett.* 2006; 47:5151–5154.(i) Lipshutz BH, Chung DW, Rich B, Corral R. *Org Lett.* 2006; 8:5069–5072.

[PubMed: 17048845] (j) Poupon JC, Boezio AA, Charette AB. *Angew Chem Int Ed*. 2006; 45:1415–1420. (k) Hagiya K, Muramoto N, Misaki T, Sugimura T. *Tetrahedron*. 2009; 65:6109–6114.

7. 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).
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.

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

^aProduct obtained were >95% pure by ¹H and ¹³C NMR.