EurJOC European Journal of Organic Chemistry

SHORT COMMUNICATION

DOI: 10.1002/ejoc.201403152

Nonsymmetrical Azocarbonamide Carboxylates as Effective Mitsunobu Reagents

Daniel P. Furkert,*[a] Benjamin Breitenbach,[a] Ludovic Juen,[a] Ina Sroka,[a] Mathilde Pantin,[a] and Margaret A. Brimble*[a]

Keywords: Synthetic methods / Azo compounds / C–O bond formation / C–N bond formation

A family of nonsymmetrical Mitsunobu reagents possessing both dialkyl amide and ester substituents was developed. These new reagents were readily prepared in a single pot from inexpensive, commercially available materials by using a scalable and environmentally friendly procedure. They were shown to exhibit activity parallel to that of diethyl azodicarboxylate/diisopropyl azodicarboxylate in a wide variety of Mitsunobu reactions. Importantly, the acyl hydrazine reaction byproducts were readily separable from the crude mixture by standard aqueous workup. In addition, the discovery of effective nonsymmetrical Mitsunobu reagents offers new directions for the ongoing development of this important reaction.

Introduction

The Mitsunobu reaction remains a mainstay in organic synthesis owing to its wide substrate scope, stereospecificity, and mild conditions.[1] It is a convenient and reliable procedure for many transformations including alcohol stereoinversion, esterification, and conversion of alcohols into amines, thioesters, and other functional groups.[2] Diethyl and diisopropyl azodicarboxylates (DEAD **1a**, DIAD **1b**; Figure 1) are currently the most widely used reagents. Close analogues (see compounds **1c**–**f**) have also been reported[3–5] to address well-known problems associated with separation of the hydrazine and/or phosphine oxide byproducts. Symmetrical azodicarbonamides **2a**–**d**[6,7] were developed to reduce purification problems and to expand the reaction scope. Cyanophosphoranes **3a** and **3b** allow the use of pronucleophiles having pK_a values up to 23.[7] Preliminary investigations into the use of catalytic amounts of Mitsunobu reagents have also been reported; these reagents can be reoxidized to regenerate the active azo compound in situ.[8]

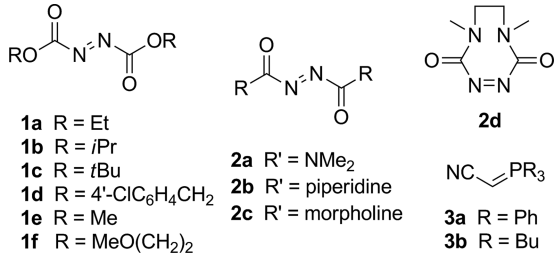


Figure 1. Mitsunobu reagents.

Results and Discussion

In the course of our synthetic work, we required dimethyl azodicarboxylate (DMAD, **1e**) for the synthesis of *N*-Boc-serine lactone **4** (Boc = *tert*-butoxycarbonyl; Figure 2); however, neither **1e** nor the literature precursor were readily available. The principle advantage of **1e** in this particular case is that the byproduct diacyl hydrazine is more readily separated from **4** by chromatography owing to the fact that its polarity is higher than that of the diacyl hydrazines derived from **1a** and **1b**. We reasoned that replacement of one of the esters in **1a**–**e** with a polar dimethylamide group should similarly confer high polarity upon the corresponding diacyl hydrazine byproducts while retaining the same reactivity. In addition, synthesis of proposed azocarbonamide carboxylate (ACC) Mitsunobu reagents **5a**–**c** appeared potentially more robust and amenable to scale up than recent azodicarboxylate preparations [e.g., di-*p*-chlorobenzyl azodicarboxylate (DCAD), **1d**[4]] that are based on carbonyl diimidazole functionalization and oxidation over two steps. We were further encouraged to conduct our study by the fact that requisite carbazates **6a**–**c** and dimethyl carbamyl chloride (**8**) are stable, inexpensive, and commercially available in bulk quantities.

Acylation of carbazates **6a**–**c** (Scheme 1, top) with dimethyl carbamyl chloride (**8**) proceeded smoothly by using a range of solvents (THF, MeCN, EtOAc) and bases (K_2CO_3, $NaHCO_3$, pyridine, Et_3N). A slightly elevated temperature (50 °C) and/or concentration (0.3 M) were required for full conversion into **7a**–**c** within 16 h. More forcing con-

[a] School of Chemical Sciences, The University of Auckland, 23 Symonds St, Auckland, New Zealand
E-mail: d.furkert@auckland.ac.nz
http://brimble.chem.auckland.ac.nz

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201403152.

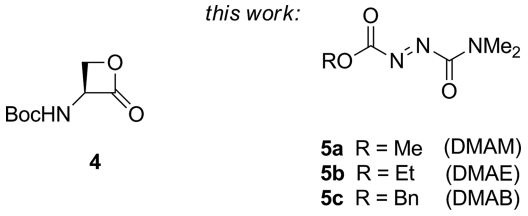
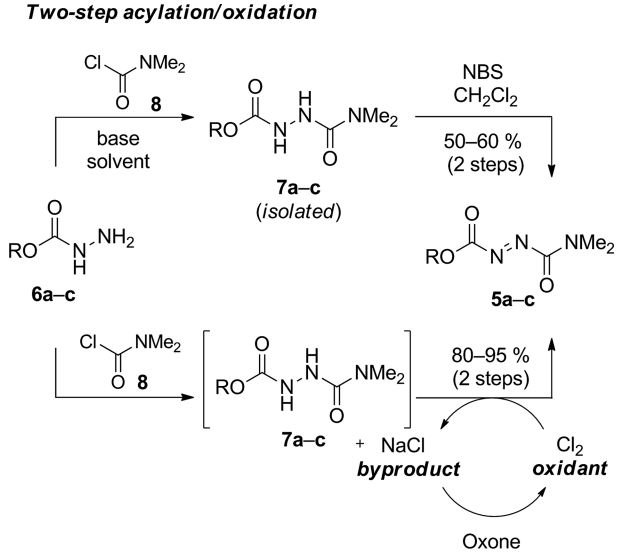


Figure 2. *N*-Boc serine lactone **4** and novel azocarbonamide carboxylate (ACC) Mitsunobu reagents **5a**–**c** prepared in this work.[9]

ditions, however, led to some formation of bis-acylated hydrazine **9** (Figure 3).



Scheme 1. Preparation of azocarbonamide carboxylates **5a**–**c**. Top: Two-step procedure. Bottom: One-pot procedure by using the NaCl byproduct generated as the in situ chloride source for oxidation of **7a**–**c**.

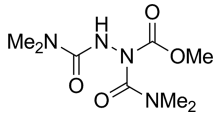


Figure 3. Structure of bis-acylated byproduct **9**.

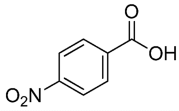
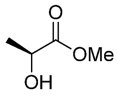
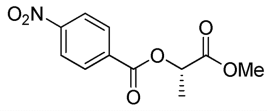
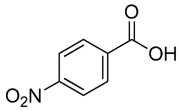
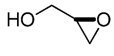
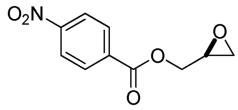
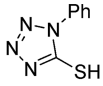
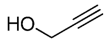
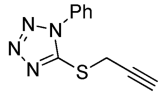
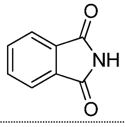
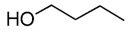
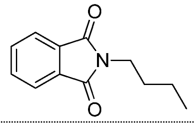
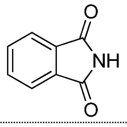
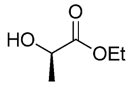
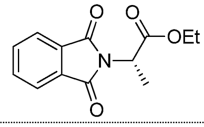
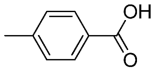
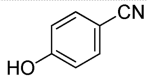
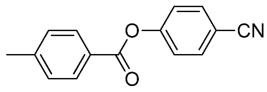
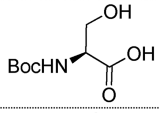
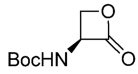
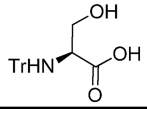
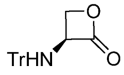
We were pleased to observe that hydrazines **7a**–**c** were relatively polar, as we had expected (R_f < 0.1; EtOAc/hexanes, 4:1), and they exhibited a significant degree of aqueous solubility.[10] During the two-step preparation, however, these attributes resulted in low yields (50–60%) of compounds **5a**–**c** owing to losses during aqueous washing of organic phases containing **7a**–**c**. Oxidation of hydrazines **7a**–**c** to corresponding azocarbonamide carboxylates **5a**–**c** was facile with the use of either bromine/pyridine or *N*-bromosuccinimide (NBS), but prior filtration to remove inorganic or protonated nitrogen salts present in the mixtures of the crude hydrazine was necessary to achieve good conversions. Additionally, chromatographic separation of succinimide was required in the latter case.

Subsequent screening of alternative oxidants revealed that both NaBr and NaCl were effective catalysts for the oxidation reaction in the presence of an excess amount aqueous Oxone through the in situ production of bromine or chlorine, respectively.[11] On the basis of this finding, it appeared that if sodium hydroxide was used as the base in the acylation step, the chloride salt byproduct present could go on to function as the oxidation catalyst in the second step. We were pleased to find that this approach worked very efficiently in practice. The final optimized conditions involved acylation of **6a**–**c** (1.0 equiv.) with dimethyl carbamyl chloride (**8**, 1.0 equiv.) and powdered sodium hydroxide (1.0 equiv.) in ethyl acetate (0.3 M) at 50 °C for 16 h. Once the acylation step was judged to be complete by TLC and/or ^{1}H NMR spectroscopy, the addition of water and Oxone rapidly effected the desired oxidation to afford **5a**–**c** in excellent yield (80–95% over two steps).

To establish the reactivity of our novel ACC reagents, a range of Mitsunobu reactions previously conducted with DEAD or DIAD were investigated by using **5a**–**c** (Table 1). Initial experiments verified that *p*-nitrobenzoic acid, commonly used for alcohol inversion, was readily esterified with both methyl lactate (Table 1, entry 1) and glycidol (Table 1, entry 2a)[12] in excellent yields. Reaction yields were observed to vary somewhat with solvent (Table 1, entries 2b and 2c). Overall, toluene and THF were found to be the most generally useful reaction solvents, depending on substrate solubility. 1-Phenyltetrazole-5-thiol, used to prepare sulfones for Julia–Kocienski olefination, underwent alkylation with propargyl alcohol in high yield (Table 1, entry 3a).[13] Tributylphosphine was found to be largely effective in place of triphenylphosphine, but in some cases it gave lower yields (Table 1, entries 3b–f).[14] In our hands, reagents **5a**–**c** performed almost identically in Mitsunobu reactions under our standard conditions (Table 1, entries 2a, 2d, 2e, 3a, 3g, and 3h). In our hands, reagent **5c** (DMAB) was generally the most convenient of the three to prepare and to use in practice.

Extension of the reaction scope to phthalimide alkylation (Table 1, entries 4 and 5)[15,16] and esterification of *p*-methylbenzoic acid (Table 1, entry 6)[17] afforded the expected products in yields close to those reported in the literature. Preparation of serine lactone **4** was identified to be problematic, and this was attributed to facile ring opening of the product, even by weak nucleophiles, and troublesome separation from Mitsunobu reagent byproducts. Widely varying yields have been reported.[18a–18c] As a result, we were pleased to find that the use of **5a** enabled successful isolation of desired lactone **4** in moderate yields after chromatography on a 1 g scale (Table 1, entry 7). The considerably more stable trityl (Tr)-protected serine lactone (Table 1, entry 8) was isolated in nearly quantitative yield under similar conditions.[19]

Table 1. Representative Mitsunobu reactions by using azocarbonamide carboxylates **5a**–**c**.

Entry	Nucleophile	Alcohol	Reagent[a]	Product	Solvent	Phosphine	Yield [%][b]
1			**5a**		CH_2Cl_2	Ph_3P	82 (98)[4]
2a			**5a**		THF	Ph_3P	93 (97)[13]
2b			**5a**		CH_2Cl_2	Ph_3P	54
2c			**5a**		PhMe	Ph_3P	38
2d			**5b**		THF	Ph_3P	80
2e			**5c**		THF	Ph_3P	89
3a			**5c**		PhMe	Ph_3P	99 (98)[14]
3b			**5a**		PhMe	nBu_3P	75
3c			**5a**		THF	Ph_3P	74
3d			**5a**		THF	nBu_3P	45
3e			**5a**		THF	Ph_3P	34
3f			**5a**		THF	nBu_3P	44
3g			**5a**		PhMe	Ph_3P	73
3h			**5b**		PhMe	Ph_3P	89
4			**5a**		THF	Ph_3P	62 (76)[15]
5			**5a**		THF	Ph_3P	56 (58)[16]
6			**5a**		THF	Ph_3P	52 (69)[17]
7		–	**5a**		THF	Ph_3P	43[c] (40)[18a]
8		–	**5a**		THF	Ph_3P	95 (95[d])[19]

[a] Alcohol (1 equiv.), nucleophile (1.1 equiv.), and phosphine (1.1 equiv.) were dissolved in the appropriate solvent at room temperature, and this was followed by the dropwise addition of specified reagent **5a**–**c**. [b] Literature yields are given in brackets. [c] –78 °C to r.t. over 18 h. [d] Reference reaction with 2-(6-chloro-1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethylaminium hexafluorophosphate (HCTU), Et_3N, CH_2Cl_2.

Conclusions

In conclusion, a new family of Mitsunobu reagents based on the azocarbonamide carboxylate (ACC) framework was developed. To the best of our knowledge, these are the first nonsymmetrical reagents employed to date for this purpose. These novel reagents are conveniently prepared in high yields in a single pot from commercially available materials and exhibit reactivity that is identical to that of commonly used DEAD and DIAD on a wide range of substrates. Importantly, the diacyl hydrazine byproducts formed during the Mitsunobu reaction are readily removed by aqueous workup. Additionally, these novel diacyl hydrazines are stable solids, and this suggests that their chromatography-free isolation and sustainable reuse is an attainable future goal. We anticipate that the convenience and economy of their preparation combined with the simple purification of the Mitsunobu reaction mixtures will make them a practically useful addition to the synthetic toolkit. Further development of nonsymmetrical Mitsunobu reagents should offer new possibilities for future development of this important reaction. Additional studies of the fundamental chemistry and practical application of nonsymmetrical azocarbonamide carboxylate compounds are ongoing in our laboratories and will be reported in due course.

Experimental Section

One-Pot Procedure for Synthesis of Azocarbonamide Carboxylate (ACC) Reagents 5a–c: A solution of carbazate **6a–c** (1 equiv.), dimethylcarbamyl chloride **8** (1 equiv.) and powdered NaOH (1 equiv.) in ethyl acetate (0.3 M) was stirred at 50 °C for 16 h open to air with a reflux condenser attached. Once the reaction was judged to be complete (TLC), the mixture was cooled to room temperature. Water (20% v/v) and Oxone (2 equiv.) were then added, and the mixture became yellow-orange. After stirring for 15–20 min, the phases were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extract was washed with saturated aqueous thiosulfate, water, and brine; dried with anhydrous $MgSO_4$; and concentrated in vacuo. Flash chromatography (hexane/ethyl acetate, 3:1; then, ethyl acetate, 100%) readily afforded the desired azocarbonamide carboxylate compounds as yellow-orange oils, yields: 83 (for **5a**), 95 (for **5b**), and 80% (for **5c**).

Representative Procedure for Mitsunobu Reactions by using 5a–c: A solution of **5a** (100 mg, 0.62 mmol, 1.2 equiv.) in THF (0.5 mL) was added to a stirred solution of glycidol (37.6 mg, 0.56 mmol), *p*-nitrobenzoic acid (93.5 mg, 0.56 mmol, 1.1 equiv.), and triphenylphosphine (140 mg, 0.56 mmol, 1.1 equiv.) in THF (1.0 mL) at room temperature. The mixture was stirred until complete by TLC (2 h) and then diluted with ethyl acetate. The organic phase was washed with water and brine to remove hydrazine byproduct **7a**, and it was then dried with anhydrous magnesium sulfate and concentrated in vacuo. An analytical sample of (oxiran-2-yl)methyl 4-nitrobenzoate for characterization was obtained by chromatography (hexanes/ethyl acetate, 9:1) as a slightly yellow powder (114 mg, 93%). Data was in agreement with that previously reported.[13]

Supporting Information (see footnote on the first page of this article): Preparation of reagents **5a–c**, characterization data, experimental procedures, and copies of the ^1H NMR and ^{13}C NMR spectra.

[1] a) O. Mitsunobu, *Synthesis* **1981**, *1*, 1–28; b) L. Kurti, B. Czako (Eds.), *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier, Burlington, MA, **2005**, p. 294–295.

[2] K. C. Kumara Swamy, N. N. Bhuvan Kumar, E. Balaraman, K. V. P. Pavan Kumar, *Chem. Rev.* **2009**, *109*, 2551–2651.

[3] a) L. A. Carpino, P. H. Terry, P. J. Crowley, *J. Org. Chem.* **1961**, *26*, 4336–4340; b) L. A. Carpino, P. J. Crowley, *Org. Synth. Coll. Vol. 5*, **1973**, p. 160; L. A. Carpino, P. J. Crowley, *Org. Synth. Coll. Vol. 44*, **1964**, p. 18.

[4] B. H. Lipshutz, D. W. Chung, B. Rich, R. Corral, *Org. Lett.* **2006**, *8*, 5069–5072.

[5] a) J. Yang, L. Dai, X. Wang, Y. Chen, *Tetrahedron* **2011**, *67*, 1456–1462; b) J. Yang, L. Dai, X. Wang, Y. Chen, *Chin. Chem. Lett.* **2011**, *22*, 1047–1050; c) K. Hagiya, N. Muramoto, T. Misaki, T. Sugimura, *Tetrahedron* **2009**, *65*, 6109–6114; d) N. Iranpoor, H. Firouzabadi, D. Khalili, S. Motevalli, *J. Org. Chem.* **2008**, *73*, 4882–4887; e) K. Hagiya, N. Muramoto, T. Misaki, T. Sugimura, *Tetrahedron* **2009**, *65*, 6109–6114.

[6] a) **2a** (TMAD): T. Tsunoda, K. Uemoto, C. Nagino, M. Kawamura, H. Kaku, S. Ito, *Tetrahedron Lett.* **1999**, *40*, 7355–7358; b) **2b** (ADDP): T. Tsunoda, Y. Yamakawa, S. Ito, *Tetrahedron Lett.* **1993**, *34*, 1639–1642; c) **2c** (ADDM): M. E. Lanning, S. Fletcher, *Tetrahedron Lett.* **2013**, *54*, 4624–4628.

[7] a) S. Ito, T. Tsunoda, *Pure Appl. Chem.* **1999**, *71*, 1053–1057, and references cited therein; b) F. Drouet, A. F. M. Noisier, C. S. Harris, D. P. Furkert, M. A. Brimble, *Eur. J. Org. Chem.* **2014**, 1195–1201.

[8] a) D. Hirose, T. Taniguchi, H. Ishibashi, *Angew. Chem. Int. Ed.* **2013**, *52*, 4613–4617; *Angew. Chem.* **2013**, *125*, 4711–4715; b) T. Y. S. But, P. H. Toy, *J. Am. Chem. Soc.* **2006**, *128*, 9636–9637; c) T. Y. S. But, J. Lu, P. H. Toy, *Synlett* **2010**, *7*, 1115–1117.

[9] The abbreviations DMAM, DMAE, and DMAB correspond to (dimethylamino)methyl, (dimethylamino)ethyl and (dimethylamino)benzylazocarbonamide carboxylates, respectively.

[10] These properties were expected to greatly simplify removal of **7a–c** from Mitsunobu reaction mixtures involving ACC reagents **5a–c**.

[11] a) P. T. Lang, A. M. Harned, J. E. Wissinger, *J. Chem. Educ.* **2011**, *88*, 652–656; b) control experiments confirmed that no reaction occurred in the absence of the halide salt.

[12] D. Camp, I. D. Jenkins, *Aust. J. Chem.* **1992**, *45*, 47–55.

[13] F. Aragozzini, E. Maconi, D. Potenza, C. Scolastico, *Synthesis* **1989**, *3*, 225–227.

[14] M. L. Blauvelt, A. R. Howell, *J. Org. Chem.* **2008**, *73*, 517–521.

[15] K. Tsuboyama, K. Takeda, K. Torii, H. Ogura, *Chem. Pharm. Bull.* **1990**, *38*, 2357–2363.

[16] O. Mitsunobu, M. Wada, T. Sano, *J. Am. Chem. Soc.* **1972**, *94*, 679–680.

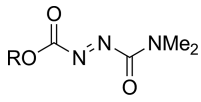
[17] V. P. Fitzjarrald, R. Pongdee, *Tetrahedron Lett.* **2007**, *48*, 3553–3557.

[18] a) S. V. Pansare, L. D. Arnold, J. C. Vederas, *Org. Synth., Coll. Vol.* 9, p. 24, **1998**; vol. 70, p. 10, **1992**; b) C. M. Taylor, S. T. De Silva, *J. Org. Chem.* **2011**, *76*, 5703–5708; c) L. D. Arnold, T. H. Kalantar, J. C. Vederas, *J. Am. Chem. Soc.* **1985**, *107*, 7105–7109.

[19] M. L. Blauvelt, A. R. Howell, *J. Org. Chem.* **2008**, *73*, 517–521.

Received: August 31, 2014
Published Online: ■

A series of nonsymmetrical Mitsunobu reagents that avoid byproduct separation problems in this useful reaction are reported. They are readily prepared by a one-pot sequence from inexpensive, commercially available materials and are shown to possess activity that is parallel to that of diethyl azodicarboxylate/diisopropyl azodicarboxylate in a wide range of synthetic transformations.



R = Me, Et, Bn

Keywords: Synthetic methods / Azo compounds / C–O bond formation / C–N bond formation

