New Synthesis of 1,1-Substituted Hydrazines by Alkylation of *N*-Acyl- or *N*-alkyloxycarbonylaminophthalimide Using the Mitsunobu Protocol

Nicolas Brosse, Maria-Fatima Pinto, and Brigitte Jamart-Grégoire*

MAEM UMR mixte CNRS-UHP no. 7567, Faculté des Sciences, Université H. Poincaré Nancy I, Bld. des Aiguillettes BP 239 F-54506 Vandoeuvre-lès-Nancy France

Brigitte.Jamart@maem.uhp-nancy.fr

Received February 17, 2000

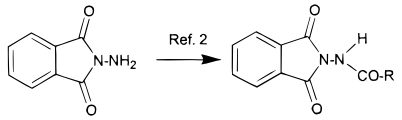
N-acyl- and *N*-alkoxycarbonylaminophthalimides are prepared using a convenient reaction and are efficiently used as acid partners in Mitsunobu reaction. This reaction allows them to be alkylated by primary, secondary or benzyl groups. Comparison of the reactivities and pK_a values of these N-substituted aminophthalimides suggest that the success of the Mitsunobu reaction in this case seems to be governed more by steric than by electronic effects. A final dephthaloylation step results in an efficient method for the preparation of 1,1-substituted hydrazines.

Introduction

The search for an efficient synthetic route for the preparation of substituted hydrazines is currently an area under active investigation as recent literature suggests.[1] For example Ragnarsson and colleagues[1h,i] have shown that multisubstituted hydrazines can be obtained from triprotected hydrazines by a stepwise synthesis that utilizes phase transfer catalysis (PTC) as an alkylation method. Specifically, primary and benzylic groups could be introduced easily using their method but fail when secondary halides are used. The corresponding substituted hydrazines are obtained via the formation of a hydrazone which must then be followed by a reduction step. The availability of a more general method for the production of substituted hydrazines is of great interest in this context.

As part of our research effort aimed at developing synthetic protocols for the preparation of protected hydrazines we have demonstrated that the direct acylation of the *N*-aminophthalimide is possible, without skeletal rearrangement, to yield compounds **2** (Scheme 1).[2] We have also shown that *N*-*tert*-butoxycarbonylaminophthalimide **2** R = O^{t}Bu can be efficiently obtained in two steps using *N*-aminophthalimide as a starting material. The compounds obtained from that study can thus be considered as one of two types which are the triacylhydrazine derivatives and the diacylcarbazates (arising from BOC protection). The structure of these compounds has a direct influence on their reactivities. In particular, compounds **2** contain three electron-withdrawing groups including two incorporated into the phthaloyl moiety, which increases the acidity of the sole proton and, concomitantly reduces steric hindrance. This structural arrangement has subsequently enabled us to develop, for the first time, a protocol for the synthesis of alkylated hydrazines[3] using compound **2** (R = O^{t}Bu) in a Mitsunobu reaction.[4]

Scheme 1



1 **2** R = O^{t}Bu, CH_3, C_6H_5, tBu,CF_3, CCl_3, 4-C_5H_4N

In this paper, we aim to show the scope and limitations of our current studies regarding the application of the Mitsunobu reaction to the synthesis of a greater range of substituted hydrazines **5** and **6**. We will demonstrate that, by using the Mitsunobu reaction step, a large variety of alkyl groups can be introduced and we will highlight the main factors that influence the successful use of this reaction for hydrazine substitution. In addition, we will present a new efficient method for the preparation of *N*-acyl- and *N*-alkyloxycarbonylaminophthalimides **2**.

Results and Discussion

Synthesis of *N*-Acyl- or *N*-Alkyloxycarbonylaminophthalimide 2. We have recently shown that the

* To whom correspondence should be addressed.

(1) (a) Cheguillaume, A.; Lehardy, F.; Bouget, K.; Baudy-Floc'h, M.; Le Grel, P. *J. Org. Chem.* **1999**, *64*, 2924−2927. (b) Ghali, N. I.; Venton, D. L. *J. Org. Chem.* **1981**, *46*, 5413−5414. (c) Gray, C. J.; Quibell, M.; Jiang, K. L.; Bagett, N. S*ynthesis* **1991**, 141−146. (d) Hoffman, R. V.; Kim, H. O. *Tetrahedron Lett.* **1990**, *31*, 2953−2956. (e) Hoffman, R. V.; Navyar, N. K. *J. Org. Chem.* **1995**, *60*, 7043−7046. (f) Vanderesse, R.; David, L.; Grand, V.; Marraud, M. *Tetrahedron Lett.* **1997**, *38*, 2669−2672. (g) Wang, Z.; Skerlji, R. T.; Bridger, G. J. *Tetrahedron Lett.* **1999**, *40*, 3543−3546. (h) Grehn, L.; Ragnarsson, U. *Tetrahedron* **1999**, *55*, 4843−4852. Mäeorg, U.; Ragnarsson, U. *Tetrahedron Lett.* **1998**, *39*, 681−684. Grehn, L.; Nyasse, B.; Ragnarsson, U. *Synthesis* **1997**, 1429−1432. (i) Mäeorg, U.; Grehn, L.; Ragnarsson, U. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2626−2627.

(2) Brosse, N.; Pinto, M. F.; Jamart-Grégoire, B. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3685−3688.

(3) (a) Brosse, N.; Pinto, M. F.; Jamart-Grégoire, B. *Tetrahedron Lett.* **2000**, *41*, 205−207. (b) One example of intramolecular Mitsunobu reaction from a substituted hydrazine has been previously reported: Iwagami, H.; Yasuda, N. *Heterocycles* **1990**, *31*, 529−536.

(4) For a review, see: Mitsunobu, O. *Synthesis* **1981**, 1−28. For recent applications of the Mitsunobu reaction see Dodd, D. S.; Kozikowski, A. P. *Tetrahedron Lett.* **1994**, *35*, 977−980. Kim, T. H; Lee G. J.; Cha, M. H *Synth. Commun.* **1999**, *29*, 2753−2758. Nikam, S. S.; Kornberg, B. E.; Rafferty, M. F. *J. Org. Chem.* **1997**, *62*, 3754−3757. Lochead, A.; Galli, F.; Jegham, S.; Nedelec, A.; George, P. *Synth. Commun.* **1999**, *29*, 799−802.

10.1021/jo000225s CCC: $19.00
Published on Web 06/09/2000

Table 1

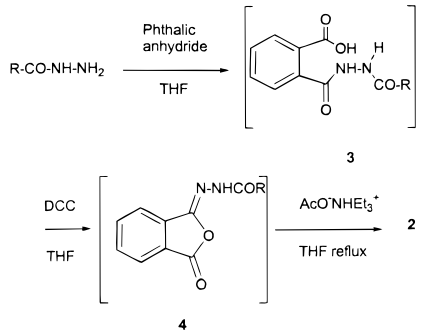
	2, yield (%)		Mitsunobu reaction				dephthaloylation		
R	method A	method B	R′	**5**	yield (%)	*Z*/*E* or *E*/*Z*	time (h)	**6**	yield (%)
CF_3	87	52[a]	CH_3	**5a**	90	20/80	70	**6a**	0
			CH_2CH_3	**5b**	85	20/80	70	**6b**	0
			CH_2Ph	**5c**	85	13/87	70	**6c**	0
			$CH(CH_3)_2$	**5d**	80[b]	*c*	70	**6d**	0
			$(CH_2)_5CH_3$	**5e**	84	*c*	70	**6e**	0
O-^{t}Bu	75[d]	82	CH_3	**5f**	97	40/60	70	**6**	65
			CH_2Ph	**5g**	83	40/60	15	**6g**	65
			$CH(CH_3)_2$	**5h**	77	40/60	7	**6h**	63
			$(CH_2)_5CH_3$	**5i**	86	*c*	24	**6i**	81
			$CH_2CH{=}CH_2$	**5j**	67	40/60	15	**6j**	89
			cyclopentyl	**5k**	85	40/60	24	**6k**	85
O−CH_2Ph	0	97	CH_3	**5l**	72	45/55	0.5	**6l**	94
			CH_2−Ph	**5m**	84	45/55	1	**6m**	90
CH_3	82	80	CH_3[e]	**5n**	85[f]	20/80	0.5	**6n**	82
			CH_2−Ph	**5o**	80	15/85	20	**6o**	73
C_6H_5	65	85	CH_3	**5p**	90	0/100	0.5	**6p**	40
			CH_2−Ph	**5q**	85	0/100	20	**6q**	92
C_5H_4N	78	80	CH_3[e]	**5r**	85[f]	0/100	20	**6r**	40[g]
			CH_2Ph	**5s**	80	0/100	20	**6s**	42
$CH(CH_3)NHZ$	72	78	CH_3	**5t**	93	20/80	20	**6t**	90
			CH_2Ph	**5u**	77	*c*	20	**6u**	85

[a] 2 equiv of phthalic anhydride and reflux conditions was used. [b] Reaction time: 1 h. [c] Not able to be determined. [d] Formation of di-*tert*-butoxycarbonylaminophthalimide which can be converted into **2** R = OtBu by reacting with CF_3COOH; see ref 2. [e] Tsunoda conditions were used.[9] [f] Reaction time: 3 h. [g] 5 equiv of $MeNH-NH_2$ was used.

formation of some *N*-acylaminophthalimides can be achieved with good yields directly from *N*-aminophthalimide (see Table 1, method A).[2] This procedure applied to singly labeled *N*-aminophthalimides constitutes a very convenient way to obtain ^{15}N singly labeled *N*-acylaminophthalimides.[2] The direct substitution of *N*-aminophthalimide has, however, subsequently proved to be limited owing to the particular behavior of this compound.[5] For example, despite considerable efforts, we were unable to obtain direct substitution of **1** by a benzyloxycarbonyl group.[2] In addition, when BOC_2O was allowed to react with **1**, a disubstituted compound was always obtained regardless of the quantities of reactants used. Another drawback was that these reactions required the use of expensive starting materials. Others have reported the synthesis of N-substituted aminophthalimides using phthalic anhydride and substituted hydrazines as starting materials;[6] however, all these methods required multistep procedures for the synthesis of specific compounds and, in most cases, used extreme reaction conditions. Taking all these factors into account, we were motivated to find alternative synthetic routes which would enable the preparation of a variety of N-substituted aminophthalimides.

Shown in Scheme 2 and in Table 1 are the results obtained using method B, which conveniently permits the general preparation of N-substituted aminophthalimides **2** using commercially avalaible hydrazides or carbazates. Method B involves the formation of two intermediates, compounds **3** and **4**, which (for R = O^{t}Bu) were isolated and identified as described in the experimental part. In the first step, the reaction of phthalic anhydride with substituted hydrazines at room temperature in THF yielded corresponding *N*-substituted-o-carboxybenzoylhydrazines **3**. Among the range of reagents described in

Scheme 2



the literature[7] for performing the cyclization of phthalamic acid derivatives into isophthalimides, we chose DCC. The addition of DCC to the reaction mixture upon the completion of the first step allowed the cyclization of compounds **3** into the corresponding isophthalimides **4**. The final step in method B is the isomerization of compounds **4** into the corresponding N-substituted aminophthalimides **2**. Good results were obtained when, following a rapid filtration to remove any dicyclohexylurea, the filtrate was then allowed to reflux in the presence of two equivalents of triethylammonium acetate.[7c] For the preparation of most substituted hydrazines, *M*ethod B gave better results than *M*ethod A with the exception of compound **2**, R = CF_3. This clean method was thus used to prepare *N*- acyl, aroyl and trifluoroacyl aminophthalimides **2** in good to very good yields and required a total reaction time of only about 2 h. Notably, method B also enabled the synthesis, for the first time, of the *N*-(*tert*-butoxycarbonyl)- and *N*-(benzyloxycarbonyl)- aminophthalimides (**2**, R = O^{t}Bu[8] and **2**, R = OCH_2-Ph respectively), from commercially avalaible corresponding carbazates.

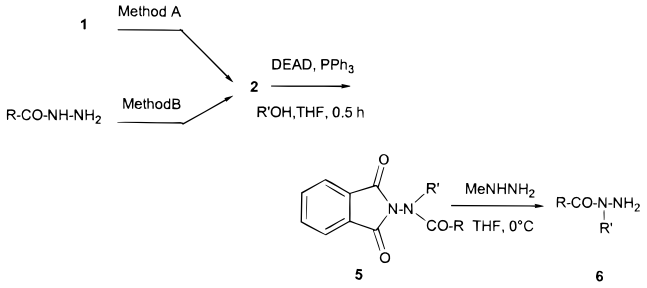
Mitsunobu Reaction: Formation of 5. As a preliminary study,[3] we showed that *N*-*tert*-butyloxycarbonylami-

(5) (a) Hearn, M. J.; Lucero, E. R. *J. Heterocycl. Chem.* **1982**, *19*, 1537−1539. (b) Hearn, M. J.; Prisch, S. B. *Org. Prep. Proced. Int.* **1981**, 421−424. (c) Drew, H. D. K.; Hatt, H. H. *J. Chem. Soc.* **1937**, 16−26.

(6) (a) El Sadek, M. M.; El Essawi, M. M.; Abdel Baky, S. A. *J. Chem. Eng. Data* **1989**, *34*, 257−259. (b) El Sadek, M. M.; Soccary, N. N. *Carbohydr. Res.* **1991**, *222*, 267−269.

(7) (a) Pyriadi, T. M. *J. Org. Chem.* **1972**, *37*, 4184−4186. (b) Roderick, W. R. *J. Org. Chem.* **1964**, *29*, 745−747. (c) Cotter, R. J.; Sauers, C. K.; Whelan, J. M. *J. Org. Chem.* **1961**, *26*, 10−21. (d) Kukolja, S.; Lammert, S. R. *J. Am. Chem. Soc.* **1975**, *97*, 5582−5583.

Scheme 3[a]



[a] Key: method A, see conditions in ref 2; method B, see conditions in Scheme 2.

nophthalimide **2**, R = O^{t}Bu, could be efficiently used in the synthesis of substituted hydrazines and/or carbazates using the Mitsunobu protocol. The results reported in Scheme 3 and Table 1 show that the range of compounds **2** used as acid partners in this reaction can be expanded compared to what we previously described. The corresponding compounds **5** were obtained with very good yield. It is interesting to note that secondary alkyl groups can also be introduced using this protocol as attested by the synthesis of compounds **5d**, **5h**, and **5k**. To circumvent any problem of purification, the synthesis of compounds **5n** and **5r** was performed by using the Tsunoda conditions[9] instead of the Mitsunobu protocol. The success of this reaction depends, however, on the presence of the phthaloyl group. It followed that all attemps to alkylate tri-*tert*-butoxycarbonylhydrazine[1i] using the Mitsunobu protocol failed. The similarity of the pK_a value for tri-*tert*-butoxycarbonylhydrazine (11.3) with those for compounds **2**, R = O^{t}Bu, CH_3 (10.9 and 11.8, respectively)[10] in water suggests that the poor reactivity of tri-*tert*-butoxylcarbonylhydrazine is not due to an electronic effect. Furthermore, previous studies[11] indicate that pK_a of approximately 9 in water is generally required for the acid partner in the Mitsunobu reaction to achieve a satisfactory result. Surprisingly, in spite of their high pK_a values, alkylation of compounds **2** using the Mitsunobu protocol was successful. This result, including the differential reactivities of compounds, led us to postulate that steric hindrance was possibly the main factor governing the reaction. The observation of two sets of resonance for some groups in ^{1}H and ^{13}C NMR spectra (see experimental part) suggested that compounds **5** were present as two isomers. This phenomenon has been described elsewhere for amide and hydrazide derivatives resulting from hindered rotation about the nitrogen to carbonyl bond thus permitting to distinguish between *Z* and *E* forms.[12] Complementary studies are under active investigation to assign resonance signals.

Dephthaloylation: Synthesis of 1-Alkylhydrazides and 1-Alkylcarbazates 6. We previously demonstrated that dephthaloylation of *N*-substituted aminophthalimides was better achieved using methylhydrazine, resulting in a very clean reaction, compared to hydrazine hydrate which gave poor results.[2,3] Methylhydrazine is known to disfavor formation of a complex with the free amine[7d] and its use in dephthaloylation for most of the compounds **5** resulted in the formation of the corresponding compounds **6** with very good yields. Curiously though, when compounds **5** were substituted by a pyridyl group, the yield decreased to 40%, even when a large excess of methylhydrazine was present. In addition, we were not able to obtain suitable conditions for dephthaloylation of trifluoroacyl forms of compounds **5**. In this case the use of methylhydrazine, as well as hydrazine hydrate, resulted in the degradation of the reaction mixture. However, using phenylhydrazine, which we had employed previously for the difficult dephthaloylation of *N*-trifluoroacylaminophthalimide,[2] the *N*-benzylaminophthalimide[5a] was obtained from compound **5c** instead of the desired compound. To circumvent this problem we thus attempted to enhance the reactivity of the imido group by converting it to isoimide as suggested in the literature.[7d,13] The corresponding isophthalimide was easily prepared; however, the subsequent use of methylhydrazine in the dephthaloylation of this compound resulted in some degradation of the reaction mixture. Finally, when performed onto starting materials **5t** and **5u**, dephthaloylation led to compounds **6t** and **6u** which could be useful in pseudopeptide synthesis.

Conclusion

We have shown that *N*-acyl and *N*-alkoxycarbonylaminophthalimides **2** can be prepared using a convenient reaction. Owing to the particular structural features where two acyl groups are incorporated into a ring, these compounds **2** have been shown to be very good acid partners in a Mitsunobu protocol thus allowing them to be alkylated with primary, secondary or benzyl groups. Comparison of the reactivities and pK_a values of compounds **2** with that of tri-*tert*-butoxycarbonylhydrazine suggested that the successful use of the Mitsunobu protocol in this case is governed more by steric than electronic effects. The subsequent use of a dephthaloylation step thus results in an efficient method for the preparation of 1,1-substituted hydrazines.

Experimental Section

General Methods. Melting points were obtained on a hot-stage apparatus and were uncorrected. NMR spectra were recorded on spectometers operating at 400 and 250 MHz. Mass spectra were performed by the ULIRS Mass Specrtroscopy Facility (the School of Farmacy, London).

General Procedure for the Preparation of *N*-Acyl- or *N*-Alkyloxycarbonylaminophthalimide 2 (Method B). Phthalic anhydride (2.96 g, 20 mmol) and carbazate or hydrazide (20 mmol) were dissolved in THF (100 mL) at room temperature under stirring. After 5 min, DCC (4.95 g, 24 mmol) is added, and the mixture is stirred for 1 h. The white precipitate of DCU is removed by filtration, acetic acid (2.4 g, 40 mmol) and Et_3N (4.05 g, 40 mmol) are added and the

(8) Some authors have mentionned the preparation in one step of **2** R=O^{t}Bu by reacting phthalic anhydride with *tert*-butylcarbazate in refluxed $CHCl_3$. In our hand this reaction which did not use cyclization reagent led to the formation of compound **3** R=O^{t}Bu instead of the desired product. Krause, J. G.; Kwon, S.; George, B. *J. Org. Chem*. **1972**, *37*, 2040−2042.

(9) Tsunoda, T.; Yamamiya, Y.; Itô, S. *Tetrahedron Lett*. **1993**, *34*, 1639−1942.

(10) The pK_a of compounds **2** was measured in aqueous solution at 25 °C by potentiometric titration of their potassium salt with hydrochloric acid. Koppel, L. K.; Koppel, J.; Leito, I.; Pihl, V.; Grehn, L.; Ragnarsson, U. *J. Chem. Res.* (S) **1994**, 212−213. *J. Chem. Res.* (M) **1994**, 1173−1186.

(11) Wada, M.; Mitsunobu, O. *Tetrahedron Lett* **1972**, 1279−1282. Koppel, I.; Koppel, J.; Degerbeck, F.; Pihl, V.; Grehn, L.; Ragnarsson, U. *J. Org. Chem*. **1991**, *56*, 7172−7174. Berrée, F.; Michelot, G.; Le Corre, M. *Tetrahedron Lett*. **1998**, *39*, 8275−8276.

(12) Lewin, A. H.; Frucht, M. *Org. Magn. Res.* **1975**, *7*, 202−225. Chakrabarty, M.; Khasnobis, S. *Synth. Commun*. **1998**, *28*, 1361−1368.

(13) Stocksdale, M. G.; Ramurthy, S.; Miller, M. J. *J. Org. Chem*. **1998**, *63*, 1221−1225.

solution is refluxed for 1 h. The mixture was poured into water, the organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$. The solid resulting from evaporation was washed several times with EtOAc−hexane.

***N*-Benzyloxycarbonylaminophthalimide 2, R = OCH$_2$Ph:** 97%; mp 140 °C; IR (NaCl) ν_{max}/cm^{-1} 3284, 3031, 1797, 1741; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.24 (s, 1H), 7.88−7.77 (m, 4H), 7.43−7.29 (m, 5H), 5.19 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 165.8, 155.9, 136.4, 135.6, 130.2, 129.1, 128.9, 128.8, 124.3, 68.0; HRMS calcd for $C_{16}H_{12}N_2O_4$ *m/z* 296.0797, found 296.0790.

L-*N*′-Benzyloxycarbonylalanine phthaloylhydrazide 2, R = Z-Ala: 78%; mp 164 °C; $[\alpha]_D = -1.5$ (*c* 1.6, CH_3COCH_3); IR (NaCl) ν_{max}/cm^{-1} 1795, 1739, 1679; ^{1}H NMR (250 MHz, $CDCl_3$) δ 11.00−10.40 (m, 1H), 8.15−7.80 (m, 4H), 7.46−7.20, (2 m, 5H), 5.11 (s, 2H), 4.50 (pt, 1H), 3.70−3.10 (m, 1H), 1.46 (d, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.2, 164.4, 163.9, 154.9, 135.8, 133.8, 128.9, 127.3, 126.8, 122.5, 65.0, 48.0, 17.6; HRMS calcd for $C_{19}H_{17}N_3O_5$ [M + NH_4^+] *m/z* 385.1525, found 385.1522.

1-*tert*-Butyloxycarbonyl-2-(2′-carboxybenzoyl)-hydrazine 3, R = O^{t}Bu: 100%; mp 186 °C; IR (KBr) ν_{max}/cm^{-1} 3600−2600;^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80−9.70 (m, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.56−7.38 (m, 3H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 168.5, 156.2, 136.8, 131.7, 131.6, 130.3, 80.3, 28.6.

***N*-*tert*-Butyloxycarbonylaminoisophthalimide 4, R = O^{t}Bu:** 82%; mp 177−179 °C (lit.[14] mp 179.5−180.5 °C); IR (KBr) ν_{max}/cm^{-1} 1795, 1720; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90−8.82 (m, 1H), 7.86 (d, 1H), 7.82 (d, 1H), 7.58 (t, 2H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 163.3, 152.5, 135.7, 135.0, 132.2, 126.4, 126.0, 122.4, 82.2, 28.5. Compounds **2**, R = O^{t}Bu, CH_3, C_6H_5, C_5H_4N, ^{t}Bu, CCl_3, CF_3 were previously described.[2]

General Procedure for the Alkylation of *N*-Acyl- or *N*-Alkoxycarbonylaminophthalimide with Alcohols (Mitsunobu Protocol). To a solution of **2** (5 mmol), PPh_3 (2 g, 7.5 mmol), and alcohol (R′OH, 7.5 mmol) in dry THF (70 mL) and under Nitrogen was added in one portion DEAD (1.3 g, 7.5 mmol) with stirring at 0−5 °C. The resulting solution was stirred for 0.5 h (monitored by TLC until completion) or 1 h in the special case of R = CF_3, R′ = ^{i}Pr and concentrated in vacuo. The residue was triturated in EtOAc, and most of the triphenylphosphine oxide and diethylhydrazinedicarboxylate was removed by filtration. The filtrate was evaporated and the residue was chromatographed on silica gel.

***N*-Methyl-*N*-trifluoromethylcarbonylaminophthalimide 5a:** 90%; mp 134 °C; IR (NaCl) ν_{max}/cm^{-1} 1802, 1756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00−7.79 (m, 4H), 3.56 and 3.35 (2 s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.9, 158.2 (q, J = 28 Hz), 135.9 and 135.5, 130.2 and 129.8, 124.9 and 124.6, 115.7 (q, J = 280 Hz), 39.5 and 37.0; HRMS calcd for $C_{11}H_7F_3N_2O_3$ *m/z* 272.0409, found 272.0406.

***N*-Ethyl-*N*-trifluoromethylcarbonylaminophthalimide 5b:** 85%; mp 122−124 °C; IR (NaCl) ν_{max}/cm^{-1} 1804, 1751, 1724; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00−7.81 (m, 4H), 3.96−3.85 (2 q, J = 7.5 Hz, 2H), 1.32 and 1.24 (2 t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 164.4, 158.4 (q, J = 30 Hz), 135.8 and 135.5, 129.5, 124.9 and 124.6, 115.8 (q, J = 285 Hz), 46.8 and 46.2, 13.1 and 12.2; HRMS calcd for $C_{12}H_{10}N_2F_3O_3$ [M + H^+] 287.0651, found 287.0644.

***N*-Benzyl-*N*-trifluoromethylcarbonylaminophthalimide 5c:** 85%; mp 86 °C; IR (NaCl) ν_{max}/cm^{-1} 1802, 1752; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00−7.77 (m, 4H), 7.47−7.23 (m, 5H), 5.10 and 5.10 (2 s, 2H); ^{13}C NMR ($CDCl_3$) 164.0, 158.4 (q, J = 28 Hz), 135.6 and 135.4, 131.9 and 130.7, 129.4, 129.3, 129.1, 124.7, 124.5, 115.8 (q, J = 286 Hz), 53.9; HRMS calcd for $C_{17}H_{12}N_2F_3O_3$ [M + H^+] 349.0788, found 349.0800.

***N*-Isopropyl-*N*-trifluoromethylcarbonylaminophthalimide 5d:** 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90−7.83, 7.80−7.73 (m, 4H), 5.43 (sept, J = 6 Hz, 1H), 1.50 (d, J = 6 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 163.9, 159.9 (q, J = 30 Hz), 135.7, 135.4, 131.1, 124.8, 123.9, 115.8 (q, J = 282 Hz), 76.1, 21.1; HRMS calcd for $C_{13}H_{12}N_2F_3O_3$ [M + H^+] 301.0787, found 301.0800.

(14) Carpino, L. A. *J. Am. Chem. Soc.* **1957**, *79*, 98−101.

***N*-Hexyl-*N*-trifluoromethylcarbonylaminophthalimide 5e:** 84%; IR (NaCl) ν_{max}/cm^{-1} 1802, 1742, 1729; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03−7.82 (m, 4H), 3.89−3.75 (m, 2H), 1.78−1.18 (m, 8H), 0.96−0.75 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 164.3, 158.0 (q, J = 25 Hz), 135.8 and 135.5, 130.0 and 129.5, 124.8 and 124.6, 115.8 (q, J = 278 Hz), 51.0, 31.6, 30.0, 28.0, 27.1, 26.4, 22.7, 14.1.

***N*-Methyl-*N*-*tert*-butyloxycarbonylaminophthalimide 5f:** 97%; mp 123 °C; IR (NaCl) ν_{max}/cm^{-1} 1793, 1731; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.98−7.73 (m, 4H), 3.34 and 3.31 (2 s, 3H), 1.52 and 1.35 (2 s, 9H); ^{13}C NMR ($CDCl_3$) δ 165.5, 165.2, 154.1, 135.1 and 135.0, 130.3 and 130.2, 124.1, 83.1 and 82.4, 38.3 and 36.8, 28.4 and 28.2; HRMS calcd for $C_{15}H_{20}N_3O_4$ [M + NH_4^+] 294.1454, found 294.1448.

***N*-Benzyl-*N*-*tert*-butyloxycarbonylaminophthalimide 5g:** 83%; mp 108 °C; IR (NaCl) ν_{max}/cm^{-1} 1796, 1737; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85−7.66 (m, 4H), 7.50−7.22 (m, 5H), 4.78 and 4.81 (2 s, 2H), 1.47and 1.45 (2 s, 9H); ^{13}C NMR ($CDCl_3$) δ 165.8 and 165.4, 153.9 and 153.7, 136.1 and 135.6, 135.1, 130.2 and 130.0, 129.4, 128.9, 128.7, 128.3, 124.1, 83.6 and 82.8, 55.0, 53.0, 28.4 and 28.3; HRMS calcd for $C_{20}H_{21}N_2O_4$ [M + H^+] 353.1501, found 353.1510.

***N*-Isopropyl-*N*-*tert*-butyloxycarbonylaminophthalimide 5h:** 77%; mp 140−143 °C; IR (NaCl) ν_{max}/cm^{-1} 1797, 1734, 1715; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99−7.77 (m, 4H), 4.66−4.50 and 4.44−4.34 (m, 1H), 1.55−1.16 (m, 15H, with 2 s at 1.53 and 1.28); ^{13}C NMR ($CDCl_3$) δ 167.2, 166.9, 152.7, 135.1, 135.0, 130.5, 130.3, 124.1, 82.9, 82.0, 51.90, 50.10, 28.6, 28.3, 21.2, 20.8; HRMS calcd for $C_{16}H_{24}N_3O_4$ [M + NH_4^+] 322.1767, found 322.1761.

***N*-Hexyl-*N*-*tert*-butyloxycarbonylaminophthalimide 5i:** 86%; IR (NaCl) ν_{max}/cm^{-1} 1796, 1733; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00−7.73 (m, 4H), 3.71−3.60 (m, 2H), 1.69−1.22 (m with 2 s at 1.51 and 1.32, 17H), 0.93−0.83 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 165.9, 153.6, 135.1 and 135.0, 130.5 and 130.3, 124.2, 83.0 and 82.3, 51.1 and 49.6, 31.9, 28.6 and 28.3, 28.1, 26.6, 22.9, 14.4; HRMS calcd for $C_{19}H_{30}N_3O_4$ [M + NH_4^+] 364.2236, found 364.2238.

***N*-Allyl-*N*-*tert*-butyloxycarbonylaminophthalimide 5j:** 67%; mp 76−78 °C; IR (NaCl) ν_{max}/cm^{-1} 1796, 1730; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.50 (m, 4H), 6.00−5.80 (m, 1H), 5.23−5.04 (m, 2H), 4.31−4.20 (m, 2H), 1.47, 1.28 (2 s, 9H); ^{13}C NMR ($CDCl_3$) δ 165.8, 165.7, 153.4, 135.1, 134.9, 132.7, 132.5, 130.3, 130.1, 124.2, 120.0, 119.6, 83.4, 82.7, 53.9, 52.0, 28.5, 28.2; HRMS calcd for $C_{16}H_{22}N_3O_4$ [M + NH_4^+] 320.1610, found 320.1617.

***N*-Cyclopentyl-*N*-*tert*-butyloxycarbonylaminophthalimide 5k:** 85%; mp 131 °C; IR (NaCl) ν_{max}/cm^{-1} 1796, 1738, 1709; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96−7.74 (m, 4H), 4.80−4.46 (m, 1H), 3.06−1.16 (m, 17H); ^{13}C NMR ($CDCl_3$) δ 166.8, 153.2, 135.1, 130.3, 124.2, 82.1, 61.3, 59.6, 30.7, 30.0, 28.6, 28.3, 23.9, 23.6; HRMS calcd for $C_{18}H_{26}N_3O_4$ [M + NH_4^+] 348.1923, found 348.1924.

***N*-Methyl-*N*-benzyloxycarbonylaminophthalimide 5l:** 72%; mp 113 °C; IR (NaCl) ν_{max}/cm^{-1} 1795, 1738; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.92−7.72 (m, 4H), 7.45−7.10 (m, 5H), 5.25 and 5.14 (2 s, 2H), 3.41 and 3.37 (2 s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.3 and 164.9, 155.1 and 155.0, 136.0, 135.2, 130.3, 130.2, 129.0, 128.8, 128.7, 128.5, 128.4, 127.6, 124.3, 69.2 and 68.6, 38.4 and 37.5; HRMS calcd for $C_{17}H_{14}N_2O_4$ *m/z* 310.0953, found 310.0947.

***N*-Benzyl-*N*-benzyloxycarbonylaminophthalimide 5m:** 84%; mp 87 °C; IR (NaCl) ν_{max}/cm^{-1} 3089, 3033, 1796, 1737; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.89−7.59 (m, 4H), 7.48−7.11 (m, 10H), 5.28 and 5.18 (2 s, 2H), 4.96 and 4.92 (2 s, 2H); ^{13}C NMR ($CDCl_3$) δ 165.0, 155.0, 136.0, 135.0, 129.9, 129.6, 129.1, 129.0, 128.8, 128.5, 128.4, 127.6, 124.2, 69.4 and 68.8, 54.8 and 53.8; HRMS calcd for $C_{23}H_{22}N_3O_4$ [M + NH_4^+] *m/z* 404.1610, found 404.1617.

***N*-Methyl-*N*-acetylaminophthalimide 5n:** 85%; mp 202 °C; IR (NaCl) ν_{max}/cm^{-1} 1795, 1740, 1710; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.97−7.76 (m, 4H), 3.49 and 3.25 (2 s, 3H), 2.30 and 1.97 (2 s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.9, 164.7, 135.5, 135.0, 130.3, 129.8, 124.5, 124.1, 39.4, 35.2, 21.1, 20.1; HRMS calcd for $C_{22}H_{30}N_3O_3$ [M + NH_4^+] *m/z* 374.1505, found 374.1505.

***N*-Benzyl-*N*-acetylaminophthalimide 5o:** 80%; mp 102 °C;^{1}H NMR (250 MHz, $CDCl_3$) δ 7.78−7.62 and 7.31−7.09 (2 m, 9H), 4.90 and 4.87 (2 s, 2H), 2.31 and 2.00 (2 s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.9, 164.8, 135.4, 134.9, 134.5, 129.9, 129.5, 129.0, 128.6, 128.5, 128.2, 124.4, 124.1, 55.6, 51.2, 21.4 and 20.8; HRMS calcd for $C_{17}H_{14}N_2O_3$ *m/z* 294.1004, found 294.1001.

***N*-Methyl-*N*-benzoylaminophthalimide 5p:** 90%; mp 155 °C; IR (NaCl) ν_{max}/cm^{-1} 1793, 1737, 1671; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12−7.81 (m, 9H), 3.37 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 173.1, 164.7, 135.4, 134.1, 130.9, 129.6, 128.5, 126.8, 124.4, 36.3; HRMS calcd for $C_{16}H_{12}N_2O_3$ *m/z* 280.0848, found 280.0842.

***N*-Benzyl-*N*-benzoylaminophthalimide 5q:** 85%; mp 133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80−7.19 (m, 9H), 5.12 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 157.4, 135.1, 128.8, 128.5, 124.2, 52.4; HRMS calcd for $C_{22}H_{30}N_3O_3$ [M + NH_4^+] *m/z* 374.1505, found 374.1505.

***N*-Methyl-*N*-isonicotinoylaminophthalimide 5r:** 85%; mp 124−126 °C; IR (NaCl) ν_{max}/cm^{-1} 1794, 1738, 1684;^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 2H), 7.34 (d, J = 6 Hz, 2H), 7.91−7.76 (m, 4H), 3.40 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.7, 164.5, 150.4, 141.9, 135.6, 129.4, 124.5, 120.7, 36.1; HRMS calcd for $C_{15}H_{11}N_3O_3$ *m/z* 281.0800, found 281.0795.

***N*-Benzyl-*N*-isonicotinoylaminophthalimide 5s:** 80%; mp 96−98 °C; IR (KBr) ν_{max}/cm^{-1} 1794, 1740, 1683;^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 6 Hz, 2H) 7.74−7.21 (m, 4H), 7.40−7.15 (m, 7H), 5.04 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 170.5, 164.5, 142.2, 135.5, 133.7, 130.3, 128.9, 124.4, 120.7, 52.3; HRMS calcd for $C_{21}H_{15}N_3O_3$ [M + H^+] *m/z* 358.1192, found 358.1197.

L-*N*′-Benzyloxycarbonylalanine-*N*-methylphthaloylhydrazide 5t: 93%; mp 133 °C; IR (NaCl) ν_{max}/cm^{-1} 1795, 1740, 1686; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00−7.76 (m, 4H), 7.40−7.25 (m, 5H), 5.82−5.73 and 5.69−5.61 (2 pd, 1H), 5.07−4.83 (m, 2H), 4.45 and 4.12 (2 q, J = 7 Hz, 1H), 3.49 and 3.28 (2 s, 3H), 1.49 and 1.28 (2 d, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.6, 164.9, 164.6, 155.6, 136.7, 135.6, 135.2, 130.3, 128.8, 128.5, 128.4, 124.4, 67.3, 47.6 and 47.0, 39.0 and 35.9, 19.5; HRMS calcd for $C_{20}H_{19}N_3O_5$ *m/z* 381.1325, found 381.1323.

L-*N*′-Benzyloxycarbonylalanine-*N*-benzylphthaloylhydrazide 5u: 77%; mp 148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90−7.73 (m, 4H), 7.51−7.15 (m, 10H), 5.80−5.68 (pd, 1H), 5.20−4.90 (m, 4H), 4.21−4.15 and 4.54−4.42 (2 m, 1H), 1.40 (d, 3H);^{13}C NMR ($CDCl_3$) δ 173.2, 165.2, 164.8, 155.9, 136.8, 136.5, 135.4, 134.0, 130.3, 130.0, 129.8, 129.1, 129.0, 128.9, 128.8, 128.7, 128.5, 128.3, 128.2, 127.2, 124.4, 67.1, 52.8, 52.2, 38.7; HRMS calcd for $C_{26}H_{23}N_3O_5$ [M + H^+] *m/z* 458.1716, found 458.1720.

General Procedure for the Dephthaloylation Reactions. To a solution of compound **5** (3 mmol) in THF (50 mL) was added at 0 °C, $MeNHNH_2$ (4.5 mmol, 225 mg). The solution was then allowed to warm to room temperature, stirred for the time indicated in Table 1, and then concentrated in vacuo. EtOAc was added, and the white precipite of phthalhydrazide was filtrated off. The filtrate was evaporated and the residue was chromatographed on neutral alumina gel.

1-Methyl-1-*tert*-butoxycarbonylhydrazine 6f: 65%; IR (NaCl) ν_{max}/cm^{-1} 3346, 1691; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02−3.82 (m, 2H), 2.87 (s, 3H), 1.28 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 155.5, 80.4, 38.4, 28.8; HRMS calcd for $C_6H_{15}N_2O_2$ [M + H^+] 147.1133, found 147.1135.

1-Benzyl-1-*tert*-butoxycarbonylhydrazine 6g: 65%; IR (NaCl) ν_{max}/cm^{-1} 3333, 1696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.22 (m, 5H), 4.55 (s, 2H), 4.20−3.80 (m, 2H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$) 157.2, 138.4, 128.8, 128.2, 127.7, 81.0, 54.8, 28.8; HRMS calcd for $C_{12}H_{19}N_2O_2$ [M + H^+] 223.1446, found 223.1445.

1-Isopropyl-1-*tert*-butoxycarbonylhydrazine 6h: 63%; IR (NaCl) ν_{max}/cm^{-1} 3341, 3227, 1797, 1738, 1686; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19−4.03 (m, 1H), 3.52 (s, 2H), 1.35 (s, 9H), 0.99 (d, 6H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 80.2, 49.0, 28.7, 19.8; HRMS calcd for $C_8H_{19}N_2O_2$ [M + H^+] 175.1446, found 175.1447.

1-Hexyl-1-*tert*-butoxycarbonylhydrazine 6i: 81%; IR (NaCl) ν_{max}/cm^{-1} 3341, 1696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 2H), 3.13 (t, J = 7 Hz, 2H), 1.26 (s, 9H), 1.15−1.05 (m, 8H), 0.70 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 157.2, 80.1, 50.5, 31.7, 28.6, 27.7, 26.5, 22.8, 14.2; HRMS calcd for $C_{11}H_{25}N_2O_2$ [M + H^+] 217.1616, found 217.1614.

1-Allyl-1-*tert*-butoxycarbonylhydrazine 6j: 89%; IR (NaCl) ν_{max}/cm^{-1} 3335 cm^{-1}, 1695; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81−5.69 (m, 1H), 5.13−5.02 (m, 2H), 3.99 (s, 2H), 3.89 (d, 2H, J = 9 Hz), 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 161.0, 133.8, 116.8, 80.8, 53.7, 28.6; HRMS calcd for $C_8H_{17}N_2O_2$ [M + H^+] 173.1290, found 173.1290.

1-Cyclopentyl-1-*tert*-butoxycarbonylhydrazine 6k: 85%; IR (NaCl) ν_{max}/cm^{-1} 3342, 1690; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (quint, J = 7.5 Hz, 1H), 4.00−3.34 (m, 1H), 1.80−1.61 (m, 6H), 1.56−1.41 (m with s at 1.47, 11H); ^{13}C NMR ($CDCl_3$) 157.0, 80.6, 58.5, 29.0, 28.9, 24.7; HRMS calcd for $C_{10}H_{21}N_2O_2$ [M + H^+] 201.1603, found 201.1601.

1-Methyl-1-benzyloxycarbonylhydrazine 6l: 94%; IR (NaCl) ν_{max}/cm^{-1} 3330, 3025, 1697;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.20 (m, 5H), 5.06 (s, 2H), 4.40−3.80 (m, 2H), 3.02 (2 s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.5, 136.9, 128.8, 128.4, 128.2, 67.8 and 67.6, 38.7; HRMS calcd for $C_9H_{12}N_2O_2$ [M + H^+] *m/z* 181.0977, found 181.0976.

1-Benzyl-1-benzyloxycarbonylhydrazine 6m: 90%; IR (NaCl) ν_{max}/cm^{-1} 3336, 3031, 1698;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.18 (m, 10H), 5.19 (s, 2H), 4.59 (s, 2H), 4.18−3.70 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 137.6, 128.9, 128.5, 128.4, 128.3, 127.8, 68.2, 54.8; HRMS calcd for $C_{15}H_{16}N_2O_2$ *m/z* 256.1211, found 256.1202.

1-Methyl-1-acetylhydrazine 6n: 82%; mp 17−20 °C (lit.[15] mp 16 °C).

1-Benzyl-1-acetylhydrazine 6o: 73%; mp 49−51 °C (lit.[16] mp 50−51 °C).

1-Methyl-1-benzoylhydrazine 6p: 40%; mp 47−49 °C (lit.[17] mp 48−50 °C).

1-Benzyl-1-benzoylhydrazine 6q: 92%; mp 68 °C (lit.[18] mp 68−70 °C).

1-Methyl-1-isonicotinoylhydrazine 6r: 40%; mp 96−97 °C (lit.[19] mp 95−96 °C).

1-Benzyl-1-isonicotinoylhydrazine 6s: 42%; mp 101 °C (lit.[19] mp 99−100 °C).

L-*N*′-Benzyloxycarbonylalanine-*N*$^\alpha$-methylhydrazide 6t: 90%; mp 118 °C; $[\alpha]_D$ = +15.75 (*c* 1.27, $CHCl_3$); IR (NaCl) ν_{max}/cm^{-1} 3407, 3324, 3225, 1710, 1661; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.24 (m, 5H), 5.80 (pd, 1H), 5.22−4.98 (m with s at 5.08, 3H), 3.87 (s, 2H), 3.13 (s, 3H), 1.31 (d, J = 7 Hz);^{13}C NMR ($CDCl_3$) δ 175.1, 155.9, 136.9, 128.7, 128.4, 128.2, 66.8, 47.3 and 47.0, 38.9, 19.2; HRMS calcd for $C_{12}H_{17}N_3O_3$ *m/z* 251.1270, found 251.1264.

L-*N*′-Benzyloxycarbonylalanine-*N*$^\alpha$-benzylhydrazide 6u: 85%; mp 148 °C; $[\alpha]_D$ = +12.04 (*c* 1.27, $CHCl_3$); IR (NaCl) ν_{max}/cm^{-1} 3405, 3325, 3220, 1715, 1657; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.12 (m, 10H), 5.79 (d, J = 8 Hz, 1H), 5.21 (m, 1H), 5.05 (s, 2H), 4.76 and 4.56 (2 d, J = 15 Hz, 2H), 3.70−3.52 (m, 1H), 1.38 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 175.4, 156.1, 137.1, 135.5, 128.4, 128.5, 128.8, 129.4, 129.5, 67.0, 53.7, 47.7, 19.4; HRMS Calcd for $C_{18}H_{21}N_3O_3$ [M + H^+] *m/z* 328.1661, found 328.1665.

***N*-Benzylaminophthalimide:** 55%; mp 106 °C (lit.[5a] mp 108−110 °C).

Acknowledgment. We are grateful to the European Community for financial support (contract BMH4-CT96-1492).

JO000225S

(15) Condon, F. E. *J. Org. Chem.* **1972**, *37*, 3608−3615.
(16) Ronco, K.; Erlenmeyer, H. *Helvetica Chim. Acta* **1956**, *39*, 124−125.
(17) Bentley, T. W. *J. Chem. Soc., Perkin Trans. 1* **1973**, 449−453.
(18) Nakajima, M.; Anselme, J.-P. *J. Org. Chem.* **1980**, *45*, 3673−3676.
(19) Fox, H. H.; Gibas, J. T. *J. Org. Chem.* **1956**, *21*, 356−361.