A High Yielding Synthesis of *N*-Alkyl Maleimides Using a Novel Modification of the Mitsunobu Reaction

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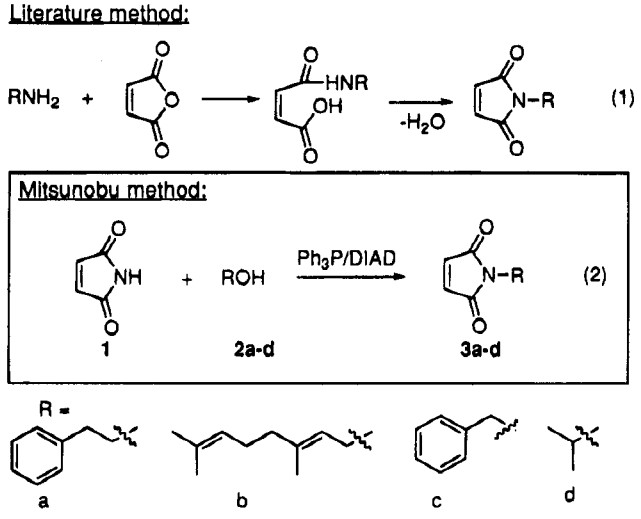
Introduction

Maleimide compounds are an important class of substrates for biological and chemical applications. In biological applications this is because they react quickly with cysteine residues[1] and thus are used as chemical probes of protein structure[2] and as linkers for conjugation of molecules to proteins.[3] These derivatives may in turn serve as immunoconjugates for cancer therapy, solid-supported enzymes for synthetic applications, or haptens for the production of antibodies.[4] In organic chemistry the maleimide functionality can be used as a synthetic platform in total synthesis due to its Michael-accepting ability and dienophilic nature.[5]



Despite this, there are few reports in the literature for the synthesis of N-substituted maleimides. Most methods involve the reaction of an amine with maleic anhydride, followed by dehydration of the intermediate maleamic acid (eq 1), usually promoted by acid.[6] This method is limited to the use of amines as starting materials and excludes those that are unstable to the dehydration conditions. Only one method has been reported for the direct N-alkylation of maleimide. In this case the corresponding silver and mercury salts were generated and allowed to react with alkyl bromides. However this method was only applied to simple *N*-alkyl maleimides.[7] In contrast to this, it has been reported from this lab that direct alkylation of alcohols with maleimide[8] is possible using Mitsunobu reaction conditions (eq 2).[9,10] This alkylation procedure is wider in scope and is complementary to the condensation/dehydration method in that the starting material is an alcohol, which may or may not contain acid sensitive functionality, rather than an amine.

The yields previously reported for the Mitsunobu synthesis of *N*-alkyl maleimides using a wide variety of alcohols[9] were low to moderate (31–73%). And, although this report was successful in demonstrating the scope of the reaction, it was felt that it would be worthwhile to try to improve the yield. Therefore, in the current study several factors were examined in order to improve the overall efficiency of the method. This goal was accomplished based on an unexpected and perhaps novel discovery concerning the effect of reagent/reactant stoichiometry and addition order on the reaction yield. Specifically, it was found that preforming the dioxaphosphorane intermediate by adding alcohol to the betaine of Ph_3P and DEAD (or DIAD)[11] followed by addition of maleimide was absolutely essential for obtaining product in a reasonable yield. Furthermore, a modified Mitsunobu procedure was developed wherein a nonreacting alcohol-additive was used to obtain yields of ≥90% for a variety of substrates.

Results and Discussion

The Mitsunobu reaction of maleimide (**1**) with phenethyl alcohol (**2a**) (eq 2) was chosen as a model for developing an optimized procedure. The first task was to determine the proper addition order of reactants and reagents. As shown in Table 1, the reaction yield was varied from 10% to 61% by simply altering the order in which the reagents were combined. For example, using a procedure commonly used for Mitsunobu-esterification (entry 1) gave a very low yield of product. It was suspected that maleimide, unlike other NH-nucleophiles,[12] was susceptible to attack by one of the reactants.

(1) Gorin, G.; Martic, P. A.; Doughty, G. *Arch. Biochem. Biophys.* **1966**, *115*, 593.

(2) For examples see: (a) Corrie, J. E. T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2975. (b) Kunicki, T. J.; Nugent, D. J.; Piotrowicz, R. S.; Lai, C.-S. *Biochemistry* **1986**, *25*, 4979.

(3) (a) Wong, S. S. *Chemistry of Protein Conjugation and Cross-linking*; CRC Press: Boca Raton, 1991. (b) Smyth, G. E.; Colman, R. F. *J. Biol. Chem.* **1991**, *266*, 14918.

(4) For recent examples and reviews see: (a) Janda, K. D.; Ashley, J. A.; Jones, T. M.; McLeod, D. A.; Schloeder, D. M.; Weinhouse, M. I. *J. Am. Chem. Soc.* **1990**, *112*, 8886. (b) Pai, L. H.; Pastan, I. *JAMA* **1993**, *269*, 78. (c) Rusiecki, V. K.; Warne, S. A.; *Biorg. Med. Chem. Lett.* **1993**, *3*, 707.

(5) For recent examples see: (a) Baldwin, S. W.; Greenspan, P.; Alaimo, C.; McPhail, A. T. *Tetrahedron Lett.* **1991**, *32*, 5877. (b) Arai, Y.; Matsui, M.; Fujii, A.; Kontani, T.; Ohno, T.; Koizumi, T.; Shiro, M.; *J. Chem. Soc., Perkin Trans 1* **1994**, 25. (c) Grigg, R.; Surendrakumar, S.; Thianpatanagul, S.; Vipond, D. *J. Chem. Soc., Perkin Trans 1* **1988**, 2693.

(6) (a) Metha, N. B.; Phillips, A. P.; Lui, L. F.; Brooks, R. E. *J. Org. Chem.* **1960**, *25*, 1012. (b) Rich, D. H.; Gesellechen, P. D.; Tong, A.; Cheung, A.; Buckner, C. K. *J. Med. Chem.* **1975**, *18*, 1004. (c) Keller, O.; Rudinger, J. *Helv. Chim. Acta.* **1975**, *58*, 531. (d) Gill, G. B.; James, G. D.; Oates, K. V.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2567. (e) Meyers, A. I.; Lefkar, B. A.; Sowin, T. J.; Westrum, L. J. *J. Org. Chem.* **1989**, *54*, 4243. (e) Rangnekar, V. M.; Bhamaria, R. P.; Khadse, B. G. *Ind. J. Chem.* **1986**, *25B*, 342. (f) Miller, S. A.; Chamberlin, A. R. *J. Org. Chem.* **1989**, *54*, 2502. (g) Garner, P.; Ho, W. B.; Grandhee, S. K.; Youngs, W. J.; Kennedy, V. O. *J. Org. Chem.* **1991**, *56*, 5893. (h) Braish, T. F.; Fox, D. E. *Synth. Lett.* **1992**, 979. (i) Nielson, O.; Buchardt, O. *Synthesis* **1991**, 819.

(7) Schwartz, A. L.; Lerner, L. M. *J. Org. Chem.* **1974**, *39*, 21. Compare, Minami, T.; Watanabe, K.; Hirakawa, K. *Chem. Lett.* **1986**, 2027, where the formation of the sodium salt of maleimide is reported; however, this intermediate was not characterized and *N*-alkyl maleimides were not synthesized from it.

(8) Jenner, G. *J. Mol. Catal.* **1989**, *55*, 241, reports the ruthenium-catalyzed coupling of ethanol with maleimide, although the N versus O regioselectivity for this alkylation was not determined.

(9) Walker, M. A. *Tetrahedron Lett.* **1994**, *35*, 665.

(10) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335.

(11) Abbreviations: DEAD (diethyl azodicarboxylate), DIAD (diisopropyl azodicarboxylate), DMAD (dimethyl azodicarboxylate), DBAD (dibutyl azodicarboxylate).

0022-3263/95/1960-5352$09.00/0

Table 1. Yield versus Addition Order for the Mitsunobu Reaction of Phenethyl Alcohol (2a)[a]

entry	temp °C[b]	method	addition order	% yield[c]
1	0	A	(i)**2a**/**1**, (ii) Ph_3P, (iii) DIAD	10
2	0	B	(i) Ph_3P, (ii) DIAD, (iii) **1**, (iv) **2a**	20
3	0	C	(i) Ph_3P, (ii) DIAD, (iii) **2a**/**1**	45
4	0	D	(i) Ph_3P, (ii) DIAD, (iii) **2a**, (iv) **1**	49
5	−78	D		61

[a] Stoichiometry of reagents, 1:1:1:1. [b] Temperature of reaction during the addition of reagents. [c] Isolated.

In method A, maleimide is exposed to Ph_3P, a potent nucleophile, which is capable of attacking the C=C bond.[13] In the past, researchers have resorted to preforming the Ph_3P·DIAD betaine before adding the nucleophile and alcohol in instances where the nucleophile was capable of independently reacting with Ph_3P or DIAD.[14] However, using this modification, as in method B, resulted in only a minor improvement in yield (entry 2). This was disappointing since having effectively removed free Ph_3P in this method, it now appeared that the reaction was somehow inhibited by the presence of the Ph_3P·DIAD betaine.[15] Therefore, it became necessary to consume the Ph_3P·DIAD by reaction with phenethyl alcohol at the same time as (method C), or prior to (method D), maleimide addition. This resulted in a reaction yield of 45−49% (entries 3 and 4), that could be further improved to 61% (entry 5) by starting the reaction at −78 °C and then allowing it to warm to room temperature.[16] Thus, it was found that for the Mitsunobu reaction of maleimide the proper choice of addition order of reagents is extremely important for achieving reasonable reaction yields. It is best to conduct the reaction in a manner such that maleimide (without ROH present) is not exposed to free Ph_3P or Ph_3P·DIAD.

Despite the fact that the addition order had been established, the yield was still less than optimal. Nonetheless, it was encouraging to find that all of the reduced DIAD (DIAD·H_2) could be recovered from the reaction. This indicated that it was not competing with maleimide for alcohol as had been observed for other NH-nucleophiles.[17] Most of the unreacted alcohol and maleimide were recovered as well,[18] meaning that under the conditions of method D a destructive side reaction was not consuming starting material but rather that a portion of the starting materials was simply not going on to form product.

It was initially felt that the modest yield was caused by the slow formation of the required oxyphosphonium salt intermediate. However, Hughes had shown that nucleophiles with higher pK_a's formed the activated alcohol species quickly and that the subsequent S_N2 reaction was the rate-limiting step.[19] Therefore, it was assumed that the incomplete turnover of starting materials was caused by a consumption of the oxyphosphonium salt ($Ph_3POR^+X^-$) that gave back the starting materials (**1** and **2a**) and Ph_3PO/DIAD·H_2 after workup. Careful drying of the solvent and carrying out the reaction under N_2 seemed to rule out the possibility that adventitious H_2O was causing this problem. Indeed, Jenkins,[20] Grochowski,[21] Adam,[22] Walker,[23] and Hughes all attest to the instability of the oxyphoshonium salt, although in a number of these cases byproducts involving the alcohol were observed.[24] Regardless of the exact mechanism, it was felt that the reaction might be driven to completion in the presence of excess reagents or reactants. Using method D as the "best" addition order, the effect of reagent and reactant stoichiometry was studied with the intent of improving the reaction yield.

Table 2. Yield versus Stoichiometry for the Mitsunobu Reaction of Phenethyl Alcohol (2a)[a]

entry	**2a** (equiv)	**1** (equiv)	Ph_3P (equiv)	DEAD (equiv)	**2e** (equiv)	yield %[b]
1	1.0	1.0	1.0	1.0	0.0	69
2	1.0	1.0	1.5	1.5	0.0	24
3	1.0	2.0	1.0	1.0	0.0	77
4	1.0	5.0	1.0	1.0	0.0	69
5	1.0	1.5	1.25	1.25	0.0	29
6	1.1	1.0	1.0	1.0	0.0	72
7	1.5	1.0	1.0	1.0	0.0	87
8	1.0	1.0	1.0	1.0	0.5	87
9	1.1	1.0	1.0	1.0	0.5	92

[a] Method D. [b] Isolated.

The results from these experiments are presented in Table 2 and summarized below. It was observed that DEAD gave comparable, if not slightly better, reaction yields than DIAD and was used in subsequent experiments.[25] In the presence of excess Ph_3P and DEAD (entries 2 and 5) a poor yield was obtained. This is consistent with the results observed in the previous set of experiments (Table 1, entry 2) and provides convincing evidence that maleimide is different from other NH-nucleophiles in that an improvement in yield cannot be obtained by driving the reaction to completion with excess Ph_3P/DEAD since Ph_3P·DEAD somehow inhibits the

(12) For an extensive list of NH-nucleophiles see: (a) Koppel, I.; Koppel, J.; Degerbeck, F.; Grehn, L.; Ragnarsson, U. *J. Org. Chem.* **1991**, *56*, 7172. (b) Ragnarsson, U.; Grehn, L. *Acc. Chem. Res.* **1991**, *24*, 285.

(13) Compare reference 1 for the nucleophilic lability of maleimide.

(14) Volante, R. P. *Tetrahedron Lett.* **1981**, *22*, 3119.

(15) Hughes (Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487) had observed that carboxylic acids can react with the DIAD·Ph_3P independently of alcohol thus lowering the yield of Mitsunobu esterification. This should be compared to Castro, J. L.; Matassa, V. G.; Ball, R. G. *J. Org. Chem.* **1994**, *59* , 2289 (and references cited therein) where the Ph_3P·DEAD complex forms an inert betaine with a cyclic sulfamide.

(16) The reaction yield was the same whether the reaction was stopped at 4 h or 24 h, suggesting that most of the reaction was occurring while the reaction mixture warmed to room temperature.

(17) Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D., Jr.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709.

(18) Unreacted alcohol was recovered in 25% yield as well as unreacted maleimide in 31% yield. The corresponding diisopropyl dihydrazide was recovered in 94% yield. The rest of the mass balance was recovered as an inseparable mixture consisting mainly of Ph_3PO.

(19) Hughes in ref 15, see also; (a) Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, *59*, 234. (b) Reference 12(a) where the yield of the Mitsunobu reaction is correlated with nucleophile pK_a.

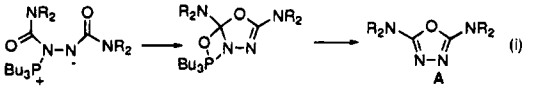
(20) Camp, D.; Jenkins, I. D. *J. Org. Chem.* **1989**, *54*, 3045.

(21) Grochowski, E.; Hilton, B. D.; Kupper, R. J.; Michejda, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 6876.

(22) Adam, W.; Narita, N.; Nishizawa, Y. *J. Am. Chem. Soc.* **1984**, *106*, 1843.

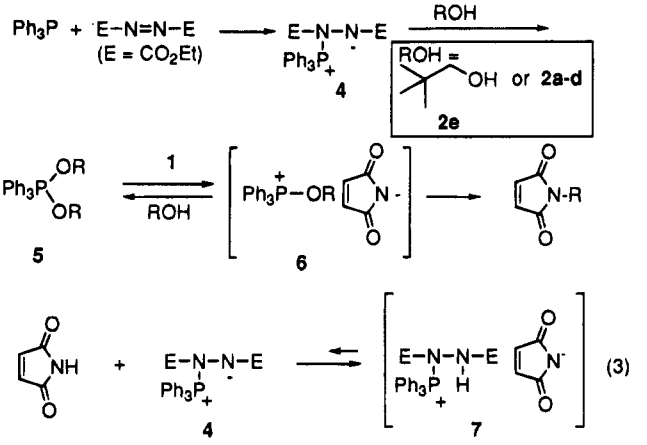
(23) Varasi, M.; Walker, K. A. M.; Maddox, M. L. *J. Org. Chem.* **1987**, *52*, 4235.

(24) Compare, Tsunoda, T.; Otsuka, J.; Yamamiya, Y.; Itô, S. *Chem. Lett.* **1994**, 539, where compound **A** was reported as a side product in the Mitsunobu amidation using TMAD and tributylphosphine according to the following mechanism (eq i):



(25) A number of other reagent systems were examined (data not shown) including the use of Bu_3P, $(PhO)_3P$ and Ph_3As in place of Ph_3P and the use of DMAD and DBAD in place of DIAD.

Scheme 1



reaction.[26] The use of excess maleimide (1.5–5.0 equiv) was examined next. However, the yield of the reaction was raised by only 8% when the amount of maleimide was increased by 100% (entry 3). When 5.0 equiv of maleimide was used (entry 4) no improvement in yield was observed. This might be due to the fact that excess nucleophile may actually slow down the S_N2 reaction.[27]

On the other hand excess alcohol was found to be very beneficial for obtaining high yields (entries 6 and 7). Thus, when 1.5 equiv of phenethyl alcohol was used in the reaction the final product was obtained in 87% yield. This result is intriguing assuming that the oxyphosphonium salt ($Ph_3POCH_2CH_2Ph^+X^-$) is the reactive intermediate in the Mitsunobu reaction. If this is true then it does not seem possible for the excess alcohol to generate more of this species than in the previous experiments since only 1.0 equiv each of Ph_3P and DEAD were used.

Nonetheless, based on the mechanistic work reported in the literature,[15,19,20–23,28] the effect of the excess alcohol can be explained in the following manner (cf. Scheme 1). In the initial reaction the betaine **4** is formed quickly and, with alcohol present, goes on to form the dioxaphosphorane **5** along with unreacted **4**.[23,29] The nucleophile (i.e. maleimide), upon addition, allows the equilibration of **5** and **6**. Under these circumstances, the excess phenethyl alcohol could improve the yield of the reaction by consuming leftover **4** which, as suggested before, inhibits the reaction. As shown in eq 3, **4** might react with maleimide to form complex **7**.[30]

If this explanation is valid then the same effect should be obtained by simultaneously using 1 equiv of an alcohol that is capable of undergoing the Mitsunobu reaction in combination with a second alcohol for which the S_N2 reaction is very slow. The second, nonreacting alcohol would thus serve as a "dummy" ligand favoring the formation of the dioxaphosphorane **5**. In accordance with this prediction, it was gratifying to find that when 0.5 equiv of neopentyl alcohol (**2e**)[31] was used in combination with 1.0 equiv of phenethyl alcohol the resulting N-substituted maleimide was produced in 87% yield (Table 2, entry 8). This is exactly the same yield as when 1.5 equiv of phenethyl alcohol was used alone. Thus, the Mitsunobu procedure using method D and 0.5 equiv of neopentyl alcohol provided the optimized reaction conditions needed for the synthesis of N-substituted maleimides. In practice, the stoichiometry of reagents shown in entry 9 (i.e. 1.1 equiv of ROH) was used in order to obtain yields of greater than 90%. Note, however, that even though a slight excess of alcohol is used, both the absolute and relative amount of phenethyl alcohol left unreacted is still less than in the original procedure. This can be accomplished without increasing the amount of Ph_3P/DEAD, allowing the efficient use of reagents and reducing the quantity of byproducts produced in the reaction. This appears to be the first time that this sort of approach has been reported in the literature.

Table 3. Synthesis of *N*-Alkyl Maleimides 3b–d

entry	alcohol	product	yield %[a]
1	**2b**	3b	90
2	**2c**	**3c**	87
3	**2d**	**3d**	83

[a] Isolated.

This procedure was applied to a number of other alcohols. As seen in Table 3, good yields were obtained using primary and secondary alcohols. Note that the yields reported in the literature for the synthesis of **3a** and **3c**, starting from the corresponding amines, are 71% and 73%, respectively, which are less than the yields obtained using the Mitsunobu procedure.[6e] Also, *N*-geranylmaleimide (**3b**) was obtained in higher yield (90%) using the modified procedure than the corresponding *N*-phthaloyl derivative using standard conditions (yield = 37%).[32] The only limitation appears to be that alcohols which are prone to elimination do not give high yields of product (data not shown). Despite this, the procedure is a general method for the high yielding synthesis of N-substituted maleimides and has permitted the synthesis, in this lab, of compounds which would have been difficult using the maleic anhydride/amine method.[33]

Experimental Section

Reactants and reagents were purchased from appropriate commercial sources and except for 2-propanol, which was dried over CaH_2, were used without further purification. All reactions were carried out under a N_2 atmosphere using anhydrous THF (Na/benzophenone) as solvent.

1-(2-Phenylethyl)-1*H*-pyrrole-2,5-dione (3a). A 250 mL round bottom flask was charged with Ph_3P (2.70g, 10.3 mmol) to which was added 70 mL of THF. The resulting clear solution was cooled to −78 °C. DEAD (1.63 mL, 10.3 mmol) was added over 2–3 min. The yellow reaction mixture was stirred 5 min after which phenethyl alcohol (1.36 mL, 11.3 mmol) was added over 1 min and stirred for 5 min. Neopentyl alcohol (0.50 g, 5.7 mmol) and maleimide (1.00 g, 10.3 mmol) were added sequentially to the reaction mixture as solids. The resulting suspension was allowed to remain at −78 °C for 5 min during which time most of the maleimide dissolved. The cooling bath was then removed, and the reaction was stirred overnight at ambient temperature. TLC indicated complete consumption of maleimide. The clear solution was concentrated to approximately 1/4

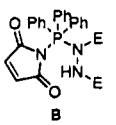
(26) For selected examples of other NH-nucleophiles giving high yields in the presence of excess reagent see: (a) Sammes, P. G.; Dean, T. *J. Chem. Soc., Perkin Trans. 1* **1989**, 655. (b) Dodd, D. S.; Kozokowski, A. P. *Tetrahedron Lett.* **1994**, *35*, 977.

(27) Cf. Hughes in ref 15.

(28) Crich, D.; Dyker, H.; Harris, R. J. *J. Org. Chem.* **1989**, *54*, 257.

(29) Pautard-Cooper, A.; Evans, S. A., Jr. *J. Org. Chem.* **1989**, *54*, 2485.

(30) This complex may be better represented as **B**:



B

(31) This substrate was shown by Jenkins (ref 20) to not undergo the S_N2 substitution reaction.

(32) Vig, O. P.; Trehan, I. R.; Kad, G. L.; Ghose, J. *Ind. J. Chem.* **1983**, *22B*, 515.

(33) Walker, M. A. Manuscript in preparation.

of the original volume under vacuum then applied to a silica gel column (2 in. × 8 in.) and eluted with 5:1 hexanes/EtOAc to yield, after removing solvent, 1.92 g (90%) of **3a** as a solid mp 110–111 °C (lit.[6e] 112 °C). ^{1}H NMR (300 MHz): δ 2.87 (dd, 2, J = 7.4), 3.74 (dd, 2, J = 7.3), 6.62 (s, 2), 7.24 (m, 5). ^{13}C NMR (75 MHz): δ 34.50, 39.09, 126.68, 128.56, 128.82, 134.02, 137.83, 170.55. MS (DCI): 202 (MH^+).

1-(3,7-Dimethyl-2,6-octadienyl)-1*H*-pyrrole-2,5-dione (3b). Solid mp 46–47 °C. ^{1}H NMR (300 MHz): δ 1.56 (s, 3), 1.65 (s, 3), 1.75 (s, 3), 2.02 (m, 4), 4.10 (d, 2, J = 6.9), 5.03 (m, 1), 5.15 (m, 1), 6.66 (s, 2). ^{13}C NMR (75 MHz): δ 16.26, 17.65, 25.65, 26.26, 35.59, 39.41, 117.91, 123.75, 131.71, 134.12, 140.50, 170.54. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C,71.89; H, 8.09; N, 5.95.

1-(Phenylmethyl-1*H*-pyrrole-2,5-dione (3c). Solid mp 68–69 °C (lit.[6h] 69–70 °C). ^{1}H NMR (300 MHz): δ 4.65 (s, 2), 6.68 (s, 2), 7.27 (m, 5). ^{13}C NMR (75 MHz): δ 41.40, 127.86, 128.38, 128.68, 134.19, 136.19, 170.41. MS (CDI) 188 (MH^+).

1-(1-Methylethyl)-1*H*-pyrrole-2,5-dione (3d). Oil (lit.[34] solid mp 27 °C). ^{1}H NMR (300 MHz): δ 1.32 (d, 6, J = 6.9), 4.15 (hept, 1, J = 6.9), 6.58 (s, 2). ^{13}C NMR (75 MHz): δ 19.99, 42.77, 133.84, 170.70.

JO950562E

(34) Takatori, K.; Hasegawa, T.; Nakano, S.; Kitamaura, J.; Katao, N. *Microbiol. Immunol.* **1985**, *29*, 1237.