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A new method for the synthesis of functionalized maleimides

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Abstract—An effective route to novel maleimides is described, which involves the reaction of an enamine derived from the addition of a secondary amine to a dialkyl acetylenedicarboxylate with an arylsulfonyl isocyanate. These maleimides in solution indicate dynamic NMR because of restricted rotation around the carbon–nitrogen bond, resulting from conjugation of the side-chain nitrogen with the adjacent α,β-unsaturated ester group.

In recent years *N*-substituted maleimides and 5-ylidenepyrrol-2(5*H*)-ones have received growing attention, since the former have potential utility as fluorescent reagents for labeling different mutant proteins[1] and the latter have interesting features associated with regioselective synthesis when different substituents are bonded to positions 3 and 4 of the skeleton.[2,3] Fused or functionalized maleimides are synthetically useful intermediates for the preparation of polycyclic and fused pyridazine derivatives.[4,5] They are also active as dienophiles in Diels–Alder reactions or as 1,3-dipolar reagents.[6,7] Substituted maleimides are a convenient molecular system for the production of thermally cured and/or photo cured polymers with a wide range of properties and applications. In addition, substituted maleimides are intermediate in the cross linking reactions of PMR-15, a leading candidate for high temperature resins for aerospace applications.[8] The majority of methods reported for the synthesis of maleimides are based on the reactions of the corresponding maleic anhydride with an amine or ammonium acetate.[9,10] Similarly, the reaction of maleamic acid with Et_3N in either toluene or benzene, yielding *N*-maleoylamino esters, can be considered as being in the same class as the previous reaction.[11,12] There is one report on the synthesis of *N*-alkylmaleimides using alkylamines, maleic anhydride and cobalt naphthenate as a catalyst.[1]

Enaminones are widely used building blocks for the synthesis of various organic compounds,[13] especially for natural bioactive substances and their analogs.[14] Enamines are also important intermediates for carbon–carbon bond formation in both organic chemistry and the biological world. In organic synthesis, pyrrolidines are used to form enamines efficiently from carbonyl compounds.

Herein, we report a simple one-pot reaction between enamines, derived from the addition of diethylamine or morpholine to a dialkyl acetylenedicarboxylate, and an arylsulfonyl isocyanate leading to maleimide derivatives[15] **3** or **4** (Schemes 1 and 2).

Compound **3** apparently result from the initial addition of diethylamine to the acetylenic system and subsequent attack of the resulting reactive enamine **5** on the arylsulfonyl isocyanate[16,17] to yield betaine **6**, which cyclizes, to produce **7**. Finally, deprotonation with alkoxide gives maleimide **3** (Scheme 3).

^1H and ^{13}C NMR spectra of the crude precipitate clearly indicated the formation of alkyl 4-(diethylamino)-2,5-dioxo-1-(arylsulfonyl)-2,5-dihydro-1*H*-pyrrole-3-carboxylates **3**. Any products other than **3** could not be detected. The mass spectrum of **3d** displayed the molecular ion peak at 394 *m*/*z*, which is consistent with the structure, ethyl 4-(diethylamino)-1-[(4-methylphenyl)sulfonyl]-2,5-dioxo-2,5-dihydro- 1*H*-pyrrole-3-carboxylate. The IR spectrum of **3d** exhibited absorption bands due to the carbonyl groups of the maleimide ring[18] at 1769 and 1694 cm^{-1} and an ester group at 1727 cm^{-1}, the absorption bands of the sulfonyl moiety appeared at 1378 and 1171 cm^{-1}.

Keywords: Dialkyl acetylenedicarboxylate; Diethylamine; Morpholine; Enamine; Isocyanate; Maleimide; Multicomponent reaction.
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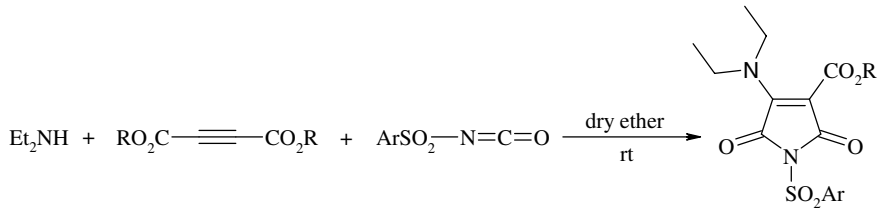


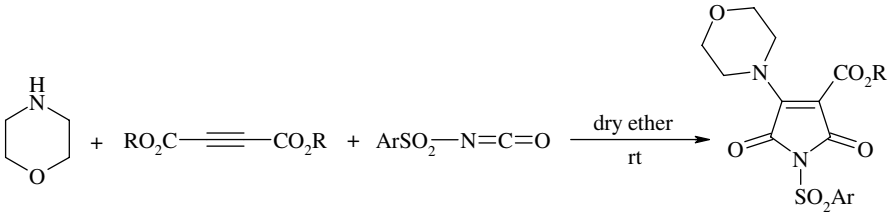
1 **2** **3**

1	R
a	Me
b	Et

2	Ar
a	Ph
b	*p*-C_6H_4

3	R	Ar	%Yield of **3**
a	Me	Ph	91
b	Et	Ph	94
c	Me	*p*-$CH_3C_6H_4$	94
d	Et	*p*-$CH_3C_6H_4$	95

Scheme 1.



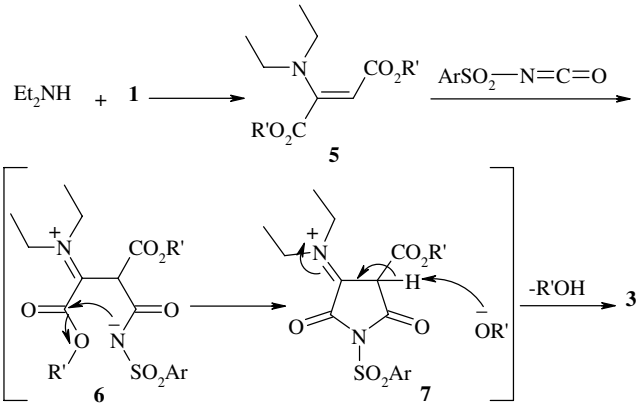
1 **2** **4**

1	R
a	Me
b	Et

2	Ar
a	Ph
b	*p*-$CH_3C_6H_4$

4	R	Ar	%Yield of **4**
a	Me	Ph	97
b	Et	Ph	98
c	Me	*p*-$CH_3C_6H_4$	98
d	Et	*p*-$CH_3C_6H_4$	95

Scheme 2.



Scheme 3.

The room temperature ^{1}H NMR spectrum of compound **3d** exhibited three sharp signals readily recognized as arising from ethoxy ($\delta = 1.25$ ppm, $^3J_{HH} = 7.1$ Hz, CH_3 and $\delta = 4.20$ ppm, $^3J_{HH} = 7.1$ Hz, OCH_2) and methyl ($\delta = 2.38$ ppm) protons. Two broad signals ($\delta = 1.15$ and 3.65 ppm) were observed for the NEt_2 group. The phenyl residues gave rise to characteristic signals in the aromatic region of the spectrum. At ca. 60 °C, the broad NEt_2 proton signals of compound **3d** became sharper ($\delta = 1.16$ ppm, $^3J_{HH} = 7.1$ Hz, CH_3 and $\delta = 3.66$ ppm, $^3J_{HH} = 7.1$ Hz, NCH_2). Decreasing the temperature resulted in splitting of the broad NEt_2 resonances into two signals for each of the methyl and methylene groups. Decreasing the temperature to 20 and 15 °C resulted in coalescence of the CH_3 and NCH_2 resonances. From the coalescence of the NCH_2 proton resonance and using the expression $k = \pi\Delta\nu/\sqrt{2}$, we calculated the first order rate constant (k) for rotation around the carbon–nitrogen bond in **3d** to be 363.5 s^{-1} at 293.16 K. Application of the absolute rate theory with a transmission coefficient of one gave a free-energy of activation $\Delta G^{\neq}$ of 57.3 ± 2 kJ mol^{-1}, where all known sources of errors were estimated and included.[19]

The ^{1}H and ^{13}C NMR spectra of compounds **3a**–**c** were similar to those of **3d**, except for the aromatic moiety, and the ester groups, which exhibited characteristic signals with appropriate chemical shifts.[15]

The reaction of an enamine derived from the addition of morpholine to a dialkyl acetylenedicarboxylate with an arylsulfonyl isocyanate gave product **4**. Structure **4d** was assigned based on elemental analysis, mass, IR, ^{1}H NMR and ^{13}C NMR spectroscopic data.

The ^{1}H and ^{13}C NMR spectra of **4d** were similar to those for **3d** except for the amine moieties, which were replaced by signals for a morpholine group.

In summary, the reaction between diethylamine or morpholine and dialkyl acetylenedicarboxylates in the presence of arylsulfonyl isocyanates provides a simple one-pot entry to the synthesis of dialkyl 4-(diethylamino)-2,5-dioxo-1-(arylsulfonyl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate or alkyl 4-morpholino-2,5-dioxo-1-(arylsulfonyl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate derivatives of potential synthetic and pharmaceutical interest. The present method carries the advantage of being performed under neutral conditions.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.04.040.

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15. The procedure for the preparation of methyl 4-(diethylamino)-2,5-dioxo-1-phenylsulfonyl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate **3a** is described as an example. To a magnetically stirred solution of 0.14 g of dimethyl acetylenedicarboxylate (1 mmol) and 0.073 g of diethylamine (1 mmol) in 5 mL dry Et_2O after 1 h was added dropwise a solution of 0.18 g of phenylsulfonyl isocyanate (1 mmol) in 3 mL of dry Et_2O at room temperature. The reaction mixture was stirred for 5 h. The resulting solid was filtered off, washed with dry methanol and dried under vacuum. Product **3a** was obtained as a yellow powder; mp 173–176 °C, 0.33 g yield 91%. IR (KBr) (ν_{max}, cm^{-1}): 1764 (CONCO), 1719 (CO_2Me), 1697 (CONCO), 1610 (C=C), 1379 and 1183 (SO_2), 1271 and 1225 (C–O of ester). Anal. Calcd for $C_{16}H_{18}N_2O_6S$ (366.39): C, 52.45; H, 4.95; N, 7.65. Found: C, 52.5; H, 5.0; N, 7.6. ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.07$ (3H, t, $^3J_{HH} = 6.3$ Hz, NCH_2CH_3), 1.23 (3H, t, $^3J_{HH} = 5.9$ Hz, NCH_2CH_3), 3.50 (2H, q, $^3J_{HH} = 6.6$ Hz, NCH_2CH_3), 3.83 (2H, q, $^3J_{HH} = 6.9$ Hz, NCH_2CH_3), 3.76 (3H, s, OCH_3), 7.53 (2H, t, $^3J_{HH} = 7.3$ Hz, $2CH_{meta}$ of C_6H_5), 7.66 (1H, t, $^3J_{HH} = 6.8$, CH_{para} of C_6H_5), 8.06 (2H, d, $^3J_{HH} = 7.4$ Hz, $2CH_{ortho}$ of C_6H_5). ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 11.55$ (NCH_2CH_3), 14.05 (NCH_2CH_3), 48.20 (NCH_2CH_3), 49.21 (NCH_2CH_3), 52.87 (OCH_3), 93.51 (*C*–CO_2Me), 128.22 ($2CH_{ortho}$ of C_6H_5), 129.38 ($2CH_{meta}$ of C_6H_5), 134.85 (C_{ipso} of C_6H_5), 137.54 (CH_{para} of C_6H_5), 146.70 (*C*–NEt_2), 160.38 (NCO), 162.16 (NCO), 163.34 (CO_2Me). MS (EI, 70 eV): *m*/*z* (%) = 367 (M^++1, 1), 366 (M^+, 3), 335 (20), 225 (10), 193 (100), 94 (16), 77 (88), 51 (14). Compound **4a**: yellow powder, mp 227–230 °C, 0.37 g yield 97%. IR (KBr) (ν_{max}, cm^{-1}): 1764 (CONCO), 1727 (CO_2Me), 1686 (CONCO), 1605 (C=C), 1379 and 1174 (SO_2), 1273 and 1220 (C–O of ester). Anal. Calcd for $C_{16}H_{16}N_2O_7S$ (380.37): C, 50.52; H, 4.24; N, 7.36. Found: C, 50.5; H, 4.2; N, 7.4. ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 3.45$ (2H, t, $^3J_{HH} = 4.1$ Hz, NCH_2CH_2O), 3.80 (3H, s, OCH_3), 3.84 (2H, t, $^3J_{HH} = 4.2$ Hz, NCH_2CH_2O), 3.87 (2H, t, $^3J_{HH} = 4.1$ Hz, OCH_2CH_2N), 4.23 (2H, m, OCH_2CH_2N), 7.58 (2H, t, $^3J_{HH} = 7.2$ Hz, $2CH_{meta}$ of C_6H_5), 7.72 (1H, t, $^3J_{HH} = 7.0$ Hz, CH_{para} of C_6H_5), 8.10 (2H, t, $^3J_{HH} = 7.8$ Hz, $2CH_{ortho}$ of C_6H_5). ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 49.66$ (NCH_2CH_2O), 52.59 (OCH_3), 53.61 (NCH_2CH_2O), 66.66 (NCH_2CH_2O), 66.92 (NCH_2CH_2O), 93.95 (*C*–CO_2Me), 128.30 ($2CH_{ortho}$ of C_6H_5), 129.44 ($2CH_{meta}$ of C_6H_5), 135.00 (C_{ipso}–SO_2), 137.39 (CH_{para} of C_6H_5), 149.85 (*C*–NCH_2CH_2O), 160.68 (NCO), 161.55 (NCO), 162.46 (CO_2Me). MS (EI, 70 eV): *m*/*z* (%) = 380 (M^+, 3), 349 (2), 239 (18), 207 (100), 179 (19), 161 (1), 138 (3), 112 (3), 111 (10), 94 (9), 77 (49), 59 (14), 51 (21).
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