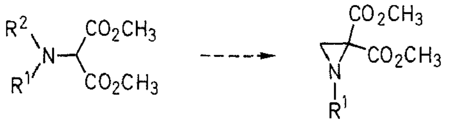
Bis(methoxycarbonyl)carbene Insertion into N–H Bonds: A Facile Route to *N*-Substituted Aminomalonic Esters

Suren Husinec, Ivan Juranic, Antonia Llobera, Alexander E. A. Porter*

Chemistry Department, University of Stirling, Stirling FK9 4LA, Scotland

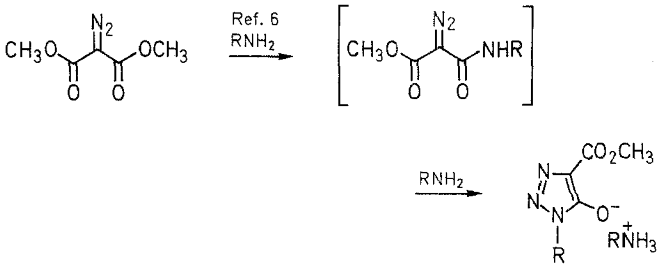
Bis(methoxycarbonyl)carbene, generated by the copper(II)-catalyzed fragmentation of 2,5-dichlorothiophenium-1-bis(methoxycarbonyl) methylide **(3)** undergoes rapid and efficient insertion into the N–H bonds of primary and secondary amines to generate *N*-substituted aminomalonic esters in good to excellent yields.

As part of our ongoing interest in the synthesis of naturally occurring pyrrolidines,[1,2] we required a series of *N*-substituted aminomalonic esters **1** as precursors to aziridines **2**[3,4] (Scheme), which could undergo subsequent cycloaddition reactions. Our initial attempts to prepare **1** from dimethyl 2-bromomalonate and the corresponding amines resulted in inseparable mixtures of alkylated products. Similarly attempts to alkylate dimethyl 2-aminomalonate by reaction with alkyl halides resulted in polyalkylation, and thus neither method represented a practical route to these simple compounds.



1 **2**

An attractive approach involving the insertion of bis(methoxycarbonyl)carbene into the N−H bond of alkylamines was conceived. Thus it is known that ethoxycarbonylcarbene, generated by the rhodium(II) acetate catalyzed decomposition of ethyl diazoacetate readily inserts into the N−H bonds of primary amines in excellent yield.[5] Logically, extension of this reaction to the use of dimethyl diazomalonate should furnish the desired *N*-substituted aminomalonates. Although aniline reacts slowly with dimethyl diazomalonate to give moderate yields of dimethyl *N*-phenylaminomalonate, the reaction of dimethyl diazomalonate with primary aliphatic amines results in the rapid formation of alkylammonium salts of 5-hydroxy-1,2,3-triazoles.[6] This reaction is believed to involve the initial reaction of the amine with one of the ester groups to generate the diazoamide, which then cyclizes under the basic reaction conditions.



We have previously demonstrated that 2,5-dichlorothiophenium-1-bis(methoxycarbonyl)methylide (**3**) undergoes carbenic

Table. *N*-Substituted Dimethyl Aminomalonates **1a**–**k** Prepared

Product	R^1	R^2	Reaction Time (min)	Yield[a] (%)	Molecular Formula[b]	IR ($CHCl_3$)[c] ν(cm^{-1})	^1H-NMR ($CDCl_3$/TMS)[d] δ, J(Hz)	MS (70eV)[e] m/z (%)
2a	H	Ph	30	93	$C_{11}H_{13}NO_4$ (223.2)	3415, 3010, 2960, 1764, 1744, 1230–1205	3.70 (s, 6H); 4.75 (br, 2H); 6.85 (5H, m)	223 (22)
2b	H	CH_2Ph	10	76	$C_{12}H_{15}NO_4$ (237.25)	3375, 3000–2800, 1730–1740, 1300–1120	2.55 (br, 1H); 3.7 (s, 6H); 3.72 (s, 2H); 4.1 (s, 1H); 7.3 (s, 5H)	237 (25.9)
2c	H	$CH(CH_3)Ph$	10	69	$C_{13}H_{17}NO_4$ (251.3)	3350, 3150–2900, 1740, 1350–1150	1.35 (d, 3H, J = 7); 3.67 (s, 3H); 3.76 (s, 3H); 3.6–4.0 (m, 2H); 7.3 (s, 5H)	251 (18.6)
2d	$-(CH_2)_5-$		30	52	$C_{10}H_{17}NO_4$ (215.2)	3000–2850, 1740, 1350–1150	1.45–1.8 (m, 6H); 2.6–2.75 (m, 4H); 3.7 (s, 6H); 4.0 (s, 1H)	215 (24.9)
2e	$-CH_2CH_2OCH_2CH_2-$		30	88[f]	$C_9H_{15}NO_5$ (217.2)	3080–2875, 1735	2.85 (m, 4H); 3.8–3.96 (m, 10H); 4.15 (s, 1H)	217 (7.0)
2f	$-CH_2CH_2SCH_2CH_2-$		60	20	$C_9H_{15}NO_4S$ (233.3)	3000–2900, 1740–1735, 1280–1150	2.1–2.3 (m, 4H); 3.0–3.15 (m, 4H); 3.75 (s, 6H); 4.05 (s, 1H)	233 (21.4)
2g	CH_3	$CH(CH_2CO_2Et)_2$	5	72	$C_{15}H_{25}NO_8$ (347.4)	2980, 1730	1.31 (t, 6H, J = 7); 2.45 (m, 2H); 2.5 (s, 3H); 3.75 (s, 6H); 3.82 (m, 1H); 4.1 (q, 4H, J = 7); 4.45 (s, 1H)	347 (24.2)
2h	CH_2Ph	$CH_2(CH_2CO_2Et)_2$	5	70	$C_{21}H_{29}NO_8$ (423.45)	3020, 2990, 1730	1.22 (t, 6H, J = 7); 2.51 (m, 4H); 3.72 (s, 6H); 3.82 (m, 1H); 3.95 (s, 2H); 4.10 (q, 4H, J = 7); 4.4 (s, 1H); 7.3 (s, 5H)	–[g]
2i	H	CO_2CH_3	30	77	$C_7H_{11}NO_6$ (205.2)	3500, 2900, 1720	3.75 (s, 3H); 3.85 (s, 6H); 5.15 (d, 1H); 6.1 (br, 1H)	205 (27.6)
2j	H	*n*-Bu	10	46	$C_9H_{17}NO_4$ (203.2)	3350, 3000–2900, 1730	1.0 (t, 3H, J = 7); 1.21–1.8 (m, 4H); 3.5–3.8 (m, 3H); 3.9 (s, 6H)	–[g]
2k	H	$CH_2CH{=}CH_2$	5	58	$C_8H_{13}NO_4$ (187.2)	3350, 3000–2900, 1735–1720, 1300–1150	3.3 (m, 2H); 3.7–3.75 (br, 7H); 4.9–5.5 (m, 3H)	187 (16.8)

[a] Yields of distilled product. In view of the known propensity of α-amino acidesters to undergo dimerization to the corresponding dioxopiperazines, the products were flash distilled in a Kugelrohr apparatus with an oven temperature preset at 150°C, at 2 Torr.

[b] Satisfactory microanalyses obtained: C, H, N ±0.2.

[c] Recorded on a Shimadzu IR435 spectrometer.

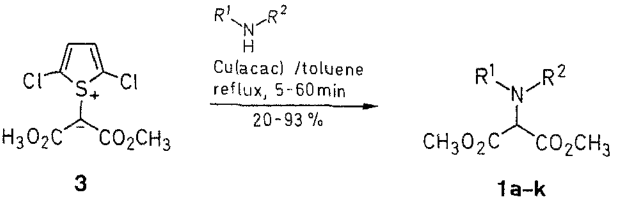
[d] All NMR spectra recorded at 90 MHz on a Perkin Elmer R32 Instrument.

[e] Recorded on a Jeol JMS D100 Instrument.

[f] Mp 59–60°C (methylcyclohexane). All of the remaining examples were pale yellow liquids at room temperature.

[g] Although no molecular ion was observed in these cases the characteristic peak M−57 corresponding to M−CO_2Me was observed.

fragmentation on thermolysis in the presence of copper(II) salts. The resultant carbenoid may be trapped with alkenes[7] or activated aromatic systems.[8] We herein report on the successful use of this reagent to bring about the insertion of bis(methoxycarbonyl)carbene into N–H bonds. The reaction of primary or secondary amines with 2,5-dichlorothiophenium-1-bis(methoxycarbonyl)methylide in refluxing toluene in the presence of copper(II)acetylacetonate is essentially complete after 30 minutes in most cases examined to date. Side reactions appear to be minimal, thus facilitating the isolation of the products (Table).



In view of the known reactivity of carbenoids generated in this way towards alkenes and activated aromatic species, the selectivity observed in these reactions is of interest. Thus aniline and benzylamine both give rise to N–H insertion products with no evidence of aromatic C–H insertion. Allylamine also appears to undergo selective N–H insertion with no evidence of cyclopropane formation. Thiomorpholine is an exception in that carbenoid insertion into the N–H bond appears to be a minor reaction pathway.

Diethyl 3-Benzylaminopentanedioate:

A mixture of diethyl 2-pentenedioate (15 g, 80 mmol) and anhydrous benzylamine (8.67 g, 81 mmol) in dry EtOH (50 mL) is heated at reflux for 18 h. The solvent is removed on a rotary evaporator. A 2 M aq. HCl solution is added to the residue until the pH of the resultant mixture reacted 1 (ca. 43 mL). The aqueous acidic solution is extracted with Et_2O (3 × 50 mL), adjusted to pH 6.0 with aqueous ammonia and again extracted with Et_2O (3 × 50 mL). The final ether extracts are combined, dried ($MgSO_4$), filtered and evaporated to dryness on a rotary evaporator. The crude product is purified by column chromatography over silica gel to give a pale yellow oil; yield: 13.8 g (59 %).

$C_{16}H_{23}NO_4$	calc.	C 65.51	H 7.90	N 4.78
(293.35)	found	65.31	7.86	4.75

Exact Mass: calc. 293.1643, found 293.1628.

IR (film): ν = 3430, 3050, 2980, 1725 cm^{-1}.

^{1}H-NMR ($CHCl_3$): δ = 1.25 (t, 6 H); 2.22 (br s, 1 H); 2.55 (d, 4 H); 3.81 (s, 2 H); 4.13 (q, 4 H); 7.25 (s, 5 H).

Diethyl 3-Methylaminopentanedioate:

A mixture of diethyl 2-pentenedioate (15 g, 80 mmol) and an excess of anhydrous methylamine (3 mL) in dry EtOH (50 mL) is allowed to react under the conditions described above. The reaction is worked up in an analogous manner to give a pale yellow oil; yield: 13.6 g (77 %).

$C_{10}H_{19}NO_4$	calc.	C 55.28	H 8.82	N 6.45
(217.3)	found	55.14	8.70	6.52

Exact Mass: calc. 217.2629, found 217.2681.

IR (film): ν = 3330, 2980, 1730 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.31 (t, 6 H); 1.70 (br s, 1 H); 2.43 (s, 3 H); 2.53 (d, 4 H); 3.32 (m, 1 H); 4.2 (q, 4 H).

***N*-Substituted Dimethyl Aminomalonates 1a–k; General Procedure:**

The amine (10 mmol), copper(II) acetylacetonate (25 mg) and 2,5-dichlorothiophenium-1-bis(methoxycarbonyl)methylide[9] (10 mmol) in dry toluene (25 mL) are heated at reflux in a preheated oil-bath until no ylide remained according to TLC (SiO_2/CH_2Cl_2) analysis. The toluene is removed under reduced pressure, and the residue is partitioned between 2 M aq. HCl (25 mL) and Et_2O (25 mL). The aqueous phase is neutralized by the cautious addition of an excess of solid $NaHCO_3$, extracted with CH_2Cl_2 (3 × 25 mL), dried ($MgSO_4$), filtered and evaporated to yield the crude product, which is purified by Kugelrohr distillation under reduced pressure (Table).

We thank The British Council (S. Husinec and A. Llobera) and the Serbian Research Council (I. Juranic) for financial support.

Received: 17 February 1988; revised: 6 April 1988

(1) Husinec, S., Porter, A.E.A., Roberts, J.S. Strachan, C.S. *J. Chem. Soc. Perkin Trans. 1* **1984**, 2517.
(2) Husinec, S., Porter, A.E.A., Strachan, C.H. *Collect. Czech. Chem. Commun.* **1987**, *52*, 207.
(3) Imai, N., Terao, Y., Aichiwa, K., Sekiya, M. *Tetrahedron Lett.* **1984**, *25*, 1579.
(4) Grigg, R., Surendrakumar, S., Thianpatanagul, S., Vipond, D. *J. Chem. Soc. Chem. Commun.* **1987**, 47.
(5) Paulissen, R., Hayez, E., Hubert, A.J., Teyssie, P. *Tetrahedron Lett.* **1974**, 607.
(6) Murray-Rust, P., McManus, J., Lennon, S.P., Porter, A.E.A., Rechka, J.A. *J. Chem. Soc. Perkin Trans. 1* **1984**, 713.
(7) Cuffe, J., Gillespie, R.J., Porter, A.E.A. *J. Chem. Soc. Chem. Commun.* **1978**, 641.
(8) Gillespie, R.J., Porter, A.E.A. *J. Chem. Soc. Chem. Commun.* **1979**, 50.
(9) Gillespie, R.J., Porter, A.E.A. *J. Chem. Soc. Perkin Trans. 1* **1979**, 2624.