Synthesis of Arylglycines by Reaction of Diethyl *N*-Boc-iminomalonate with Organomagnesium Reagents

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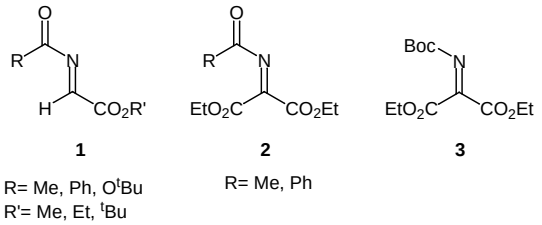
Abstract: Diethyl *N*-Boc-iminomalonate (**3**), prepared on multigram scale, served as a stable and highly reactive electrophilic glycine equivalent which reacted with organomagnesium compounds affording substituted aryl *N*-Boc-aminomalonates. Subsequent hydrolysis produced arylglycines.

Key words: amino acids, arylaminomalonates, arylglycines, imino esters, Grignard reactions

Arylglycines constitute an important class of non-proteinogenic α-amino acids.[1] Even though a great number of asymmetric synthesis of these compounds has been developed, the success has in many cases been compromised by the ease of racemization.[2] As a result, arylglycines are often synthesized in racemic form and the enantiomers are then separated.[2] The reaction of electrophilic glycine equivalents with various aromatic organometallic reagents has been widely used for this purpose.[3] Thus N-protected iminoglycinates **1** have been generated in situ by base-induced elimination of HX from the corresponding α-halo-N-protected glycinate (Figure 1).[4–6] In a typical approach the α-halo derivative is treated with two equivalents of organometallic reagent, the first effecting the elimination, and the second adding to the generated iminoglycinate. Alternatively, a tertiary amine can be used to generate the imine, but the ammonium halogenide formed then has to be removed by filtration prior to the addition of the organometallic compound. In these reactions carbamates such as *N*-Boc were preferred as protecting groups since milder conditions are required for the deprotection after C–C bond formation.[7]

Similarly, *N*-acyl-iminomalonates **2**, prepared in situ, have been reacted with C-nucleophiles.[8] In the few cases reported, *N*-acyl protection was used, requiring quite harsh conditions for the deprotection. A single example of the use of *N*-Boc-iminomalonate has been described in the literature, where the compound served as a dienophile in Diels–Alder reactions.[9]

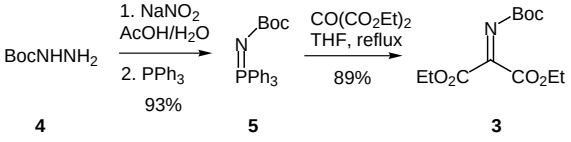
We have now shown that diethyl *N*-Boc-iminomalonate (**3**), prepared and isolated in high yields as a stable oil, is a versatile glycine equivalent. It reacted rapidly and selectively with Grignard compounds to give *N*-Boc-aminomalonates, which could be N-deprotected under mild conditions. Subsequent hydrolysis of the ester group gave access to arylglycines.



1 **2** **3**

Figure 1

Diethyl *N*-Boc-iminomalonate (**3**) was prepared on multigram scale by an aza-Wittig reaction[9,10] between *N*-Boc-triphenyliminophosphorane (**5**)[11,12] and diethyl mesoxalate (Scheme 1). The iminomalonate **3** was distillable and could be isolated as a colorless oil in 89% yield. No signs of decomposition could be observed after storage at 4 °C for several months.



4 **5** **3**

Scheme 1

A series of functionalized arylglycine derivatives **8a**–**h** was prepared by reacting imine **3** with various Grignard reagents at low temperature (Table 1). Halogen-metal exchange is a powerful tool for the preparation of functionalized organometallic species.[13–15] Thus, the aryl and heteroaryl iodides **6a**–**h** were converted into the corresponding organomagnesium compounds upon treatment with 1.1 equivalents of *i*-PrMgCl for 1 h at a temperature between –40 °C and room temperature. When a THF solution of imine **3** was added to the Grignard solution at –78 °C, the imine reacted rapidly to afford the desired adducts **7a**–**h** as the sole product. No significant difference in reactivity was observed, and all reactions were completed after 1 h at –78 °C. The addition of the organomagnesium reagents occurred selectively on the imine carbon and no by-products due to addition to the ester or the carbamate were detected by NMR and GC-MS analysis of the crude adduct **7a**–**h**. When the same reaction was performed at –40 °C, a more complex mixture of compounds

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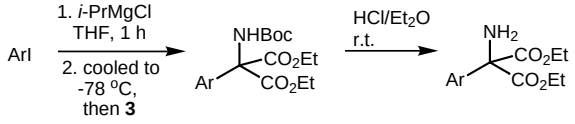
was obtained. Chromatographic purification of **7a**–**h** was hampered by a co-eluting impurity, presumably derived from the slowly decomposing excess imine **3**.[16] Therefore, the *N*-Boc group was removed directly from crude **7a**–**h** by stirring in ethereal HCl at room temperature for 12 h. After workup and basification the aminomalonate derivatives **8a**–**h** were obtained in 71–89% yields. For all crude products satisfactory elemental analyses were obtained without further purification.

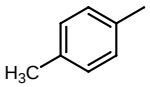
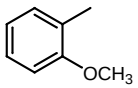
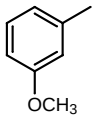
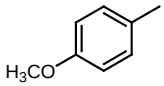
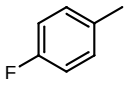
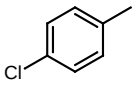
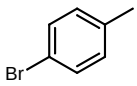
Liberation of the desired amino acid functionality could be achieved by acidic or basic hydrolysis of the diethyl malonate followed by decarboxylation, as extensively reported in the literature.[17] By way of example, intermediates **8d** and **8e** were deprotected to give the target arylglycines **9** and **10** as hydrochloride and free amino acid, respectively (Table 2). Acidic hydrolysis was carried out by refluxing **8d** and **8e** in 6 N HCl for 1 h affording **9** and **10** in 80% and 84% yield, respectively (Method A). A milder alternative is represented by the saponification using 2 N LiOH followed by decarboxylation of the malonate at 50 °C under acidic conditions (Method B). By this way the target amino acids **9** and **10** were obtained in 81% and 79% yields, respectively.

In conclusion, the reaction of diethyl *N*-Boc-iminomalonate (**3**) with organomagnesium reagents represents a versatile three-step route to racemic arylglycines. Imine **3** is stable, easily prepared on a multi-gram scale and highly reactive with organomagnesium reagents at low temperature. Main advantages of this strategy include the commercial availability of the starting aryl and heteroaryl iodides and the easy N-deprotection procedure.

Table 1 Synthesis of Arylglycine Derivatives **8**

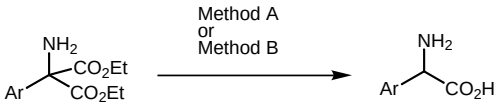


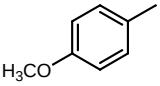
6 **7** **8**

Entry[a]	Ar	Product	Yield (%)[b]
1		**8a**	75
2		**8b**	75
3		**8c**	71
4		**8d**	79
5		**8e**	73
6		**8f**	72
7		**8g**	76
8		**8h**	89

[a] The halogen-metal exchange was performed at r.t. for entries 1–4, at 0 °C for entries 5–7, and at –40 °C for entry 8 (see experimental).
[b] Overall yields based on iodides **6**. In all cases satisfactory elemental analysis were obtained without further purification.

Table 2 Deprotection of Derivatives **8d** and **8e**



Ar	Starting Material	Product	Yield (%)
	**8d**	**9**[a]	80[c]/81[d]
	**8e**	**10**[b]	84[c]/79[d]

[a] Isolated as HCl salt, see experimental.
[b] Isolated as free amino acid after ion exchange, see experimental.
[c] Isolated yields applying Method A: 6 N HCl, 1 h, reflux.
[d] Isolated yields applying Method B: 2 N LiOH, THF, 2 h, r.t., then 1 N HCl, 50 °C, 15 min.

All reactions involving air-sensitive reagents were performed under N_2 using syringe-septum cap technique. All glassware was flame-dried prior to use. ^1H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian instrument using TMS as internal standard. Melting points are uncorrected. All solvents and reagents were of analytical grade and purchased from Aldrich or Fluka and used without further purification. THF was distilled from Na/benzophenone ketyl under N_2. Et_2O was dried over Na wire. *i*-PrMgCl solution was titrated prior to use.[18]

***N*-Boc-Triphenyliminophosphorane (5)[11]**

To a solution of *t*-butyl carbazate **4** (26.42 g, 0.2 mol) in CH_3CO_2H (80 mL) and H_2O (160 mL) cooled to 0 °C was added $NaNO_2$ (15.18 g) in portions over 15 min. The solution was stirred for 30 min at 0 °C, then extracted with Et_2O (2 × 250 mL). The combined organic layers were washed with H_2O (300 mL), quickly with sat. aq $NaHCO_3$ (200 mL), sat. aq NaCl (200 mL), and dried (Na_2SO_4). This solution was directly used in the next step. CAUTION: To avoid risks of explosion, do not warm the ethereal solution of the azide and do not concentrate to dryness! The ether solution of the *N*-Boc-azide was cooled to 0 °C, and PPh_3 (53 g, 0.2 mmol) was added in small portions while stirring. Strong evolution of nitrogen occurred during the addition of triphenylphosphine. The cooling bath was then removed and the reaction stirred for 30 min at r.t. The

formed white precipitate was filtered, washed with Et_2O and dried in vacuo (69.8 g, 92% yield); mp 148 °C (Lit.[11]148 °C).

Diethyl *N*-Boc-Iminomalonate (3)

A solution of *N*-Boc-triphenyliminophosphorane (**5**, 41.5 g, 0.11 mol) and diethyl mesoxalate 98% (17.4 g, 0.1 mol) in anhyd THF (200 mL), was refluxed at 80 ºC under N_2 for 12 h. The THF was evaporated and anhyd Et_2O (150 mL) was added to precipitate the triphenylphosphine oxide. The solid was filtered, washed with cold Et_2O, and the collected filtrate was evaporated to dryness to afford a pale yellow oil. The crude product was purified by ball-tube distillation (140 ºC, 0.45 mbar) to give pure **3** as a colorless oil (24.3 g, 89%), which was stored at 4 °C.

^{1}H NMR ($CDCl_3$): δ = 4.39 (q, 4 H, *J* = 7.2 Hz, OCOC*H*$_2$CH$_3$), 1.56 [s, 9 H, C(C*H*$_3$)$_3$], 1.37 (t, 6 H, *J* = 7.2 Hz, OCOCH$_2$C*H*$_3$).

^{13}C NMR ($CDCl_3$): δ = 161.3, 158.2, 158.0, 151.6, 84.5, 63.1, 62.9, 27.6, 13.6.

Anal. Calcd for $C_{12}H_{19}NO_6$: C, 52.74; H, 7.01; N, 5.13. Found: C, 52.89; H, 6.96; N, 5.00.

Arylglycine Derivatives 8; General Procedure

To a stirred solution of the aryl iodide **6** (4 mmol) in THF (20 mL) under N_2 at the indicated temperature, was added dropwise 2.0 M *i*-PrMgCl in THF (2.2 mL, 4.4 mmol). After 1 h the mixture was cooled to –78 ºC and a solution of the *N*-Boc-iminomalonate **3** (1.09 g, 4 mmol) in THF (2 mL) was added. Stirring was continued for 1 h at –78 ºC before quenching cold with H_2O (3 mL). The reaction mixture was allowed to warm to r.t., sat. aq NH_4Cl (20 mL) was added and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated to afford crude **7** as an oil. Crude **7** was dissolved in anhyd Et_2O (10 mL) under N_2, 2 M HCl in Et_2O was added (6 mL, 12 mmol) and stirring at r.t. was continued for 12 h. The solvents were removed in vacuo, H_2O (30 mL) was added and the mixture washed with Et_2O (3 × 10 mL). A sat. aq solution of $NaHCO_3$ was added to the water phase until reaching pH 7 and the unclear solution was extracted with Et_2O (5 × 30 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and evaporated to give the pure product **8**.

Diethyl 2-Amino-2-(4-tolyl)-malonate (8a)

Following the general procedure using 2-iodotoluene (872 mg, 4 mmol) and performing the halogen-metal exchange at r.t.

Pale yellow oil (798 mg, 75%).

^{1}H NMR ($CDCl_3$): δ = 7.46 (m, 2 H, Ar-*H*), 7.17 (m, 2 H, Ar-*H*), 4.26 (m, 4 H, OCOC*H*$_2$CH$_3$), 2.34 (s, 3 H, PhC*H*$_3$), 1.27 (t, 6 H, *J* = 7.1 Hz, OCOCH$_2$C*H*$_3$).

^{13}C NMR ($CDCl_3$): δ = 171.3, 138.1, 134.8, 128.8, 127.0, 68.9, 62.1, 20.9, 13.8.

Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.14; H, 6.97; N, 5.33.

Diethyl 2-Amino-2-(2-methoxyphenyl)-malonate (8b)

Following the general procedure using 2-iodoanisole (936 mg, 4 mmol) and performing the halogen-metal exchange at r.t.

Pale yellow oil (846 mg, 75%).

^{1}H NMR ($CDCl_3$): δ = 7.32 (ddd, 1 H, *J* = 8.1, 7.6, 1.7 Hz, Ar-*H*), 7.20 (dd, 1 H, *J* = 7.6, 1.7 Hz, Ar-*H*), 6.95 (m, 1 H, Ar-*H*), 6.92 (m, 1 H, Ar-*H*), 4.29 (m, 4 H, OCOC*H*$_2$CH$_3$), 3.81 (s, 3 H, OC*H*$_3$), 2.30 (br s, 2 H, N*H*$_2$), 1.27 (t, 6 H, *J* = 7.1 Hz, OCOCH$_2$C*H*$_3$).

^{13}C NMR ($CDCl_3$): δ = 171.1, 159.9, 129.5, 128.9, 127.4, 120.7, 111.6, 68.4, 62.0, 55.5, 13.9.

Anal. Calcd for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81; N, 4.98. Found: C, 59.53; H, 6.60; N, 4.76.

Diethyl 2-Amino-2-(3-methoxyphenyl)-malonate (8c)

Following the general procedure using 3-iodoanisole (936 mg, 4 mmol) and performing the halogen-metal exchange at r.t.

Pale yellow oil (801 mg, 71%).

^{1}H NMR ($CDCl_3$): δ = 7.28 (m, 1 H, Ar-*H*), 7.19 (br m, 1 H, Ar-*H*), 7.13 (ddd, 1 H, *J* = 7.8, 1.7, 0.9 Hz, Ar-*H*), 6.88 (ddd, 1 H, *J* = 8.1, 2.6, 0.9 Hz, Ar-*H*), 4.27 (m, 4 H, OCOC*H*$_2$CH$_3$), 3.81 (s, 3 H, OC*H*$_3$), 2.29 (br s, 2 H, N*H*$_2$), 1.28 (t, 6 H, *J* = 7.1 Hz, OCOCH$_2$C*H*$_3$).

^{13}C NMR ($CDCl_3$): δ = 171.0, 159.4, 139.3, 129.0, 119.5, 113.7, 112.8, 69.1, 62.2, 55.1, 13.8.

Anal. Calcd for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81; N, 4.98. Found: C, 59.88; H, 6.75; N, 4.82.

Diethyl 2-Amino-2-(4-methoxyphenyl)-malonate (8d)

Following the general procedure using 4-iodoanisole (936 mg, 4 mmol) and performing the halogen-metal exchange at r.t.

Pale yellow oil (866 mg, 77%).

^{1}H NMR ($CDCl_3$): δ = 7.50 (d, 2 H, *J* = 9.0 Hz, Ar-*H*), 6.88 (d, 2 H, *J* = 9.0 Hz, Ar-*H*), 4.26 (m, 4 H, OCOC*H*$_2$CH$_3$), 3.80 (s, 3 H, OC*H*$_3$), 2.35 (br s, 2 H, N*H*$_2$), 1.27 (t, 6 H, *J* = 7.1 Hz, OCOCH$_2$C*H*$_3$).

^{13}C NMR ($CDCl_3$): δ = 171.3, 159.4, 129.6, 128.3, 113.3, 68.5, 62.0, 55.0, 13.7.

Anal. Calcd for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81; N, 4.98. Found: C, 59.84; H, 6.63; N, 4.91.

Diethyl 2-Amino-2-(2-thienyl)-malonate (8e)

Following the general procedure using 2-iodothiophene (840 mg, 4 mmol) and performing the halogen-metal exchange at 0 °C.

Pale yellow oil (750 mg, 73%).

^{1}H NMR ($CDCl_3$): δ = 7.29 (dd, 1 H, *J* = 5.1, 1.2 Hz, Ar-*H*), 7.21 (dd, 1 H, *J* = 3.7, 1.2 Hz, Ar-*H*), 7.28 (dd, 1 H, *J* = 5.1, 3.7 Hz, Ar-*H*), 4.28 (m, 4 H, OCOC*H*$_2$CH$_3$), 2.55 (br s, 2 H, N*H*$_2$), 1.29 (t, 6 H, *J* = 7.1 Hz, OCOCH$_2$C*H*$_3$).

^{13}C NMR ($CDCl_3$): δ = 169.8, 141.5, 126.7, 126.3, 125.8, 66.7, 62.4, 13.6.

Anal. Calcd for $C_{11}H_{15}NO_4S$: C, 51.35; H, 5.88; N, 5.44. Found: C, 51.39; H, 5.63; N, 5.32.

Diethyl 2-Amino-2-(4-fluorophenyl)-malonate (8f)

Following the general procedure using 1-fluoro-4-iodobenzene (888 mg, 4 mmol) and performing the halogen-metal exchange at 0 °C.

Colourless oil (774 mg, 72%).

^{1}H NMR ($CDCl_3$): δ = 7.58 (m, 2 H, Ar-*H*), 7.05 (m, 2 H, Ar-*H*), 4.29 (m, 4 H, OCOC*H*$_2$CH$_3$), 2.72 (br s, 2 H, N*H*$_2$), 1.28 (t, 6 H, *J* = 7.1 Hz, OCOCH$_2$C*H*$_3$).

^{13}C NMR ($CDCl_3$): δ = 170.9, 162.7 (d, *J* = 247 Hz), 133.4, (d, *J* = 3.2 Hz), 129.1 (d, *J* = 8.3 Hz), 114.9 (d, *J* = 21.6 Hz), 68.6, 62.3, 13.8.

Anal. Calcd for $C_{13}H_{16}FNO_4$: C, 57.99; H, 5.99; N, 5.20. Found: C, 57.71; H, 5.99; N, 4.91.

Diethyl 2-Amino-2-(4-chlorophenyl)-malonate (8g)

Following the general procedure using 1-chloro-4-iodobenzene (954 mg, 4 mmol) and performing the halogen-metal exchange at 0 °C.

Pale yellow oil (866 mg, 76%).

^{1}H NMR ($CDCl_3$): δ = 7.55 (d, 2 H, *J* = 8.6 Hz, Ar-*H*), 7.33 (d, 2 H, *J* = 8.6 Hz, Ar-*H*), 4.27 (m, 4 H, $OCOCH_2CH_3$), 2.35 (br s, 2 H, NH_2), 1.28 (t, 6 H, *J* = 7.1 Hz, $OCOCH_2CH_3$).

^{13}C NMR ($CDCl_3$): δ = 170.8, 136.2, 134.3, 128.7, 128.2, 68.6, 62.4, 13.7.

Anal. Calcd for $C_{13}H_{16}ClNO_4$: C, 54.65; H, 5.64; N, 4.90. Found: C, 54.71; H, 5.55; N, 4.83.

Diethyl 2-Amino-2-(4-bromophenyl)-malonate (8h)
Following the general procedure using 1-bromo-4-iodobenzene (1.12 g, 4 mmol) and performing the halogen-metal exchange at −40 °C.

Pale yellow oil (866 mg, 89%).

^{1}H NMR ($CDCl_3$): δ = 7.45 (m, 4 H, Ar-*H*), 4.22 (m, 4 H, $OCOCH_2CH_3$), 2.32 (br s, 2 H, NH_2), 1.23 (t, 6 H, *J* = 7.1 Hz, $OCOCH_2CH_3$).

^{13}C NMR ($CDCl_3$): δ = 170.7, 136.7, 131.2, 129.0, 122.5, 68.7, 62.4, 13.8.

Anal. Calcd for $C_{13}H_{16}BrNO_4$: C, 47.29; H, 4.88; N, 4.24. Found: C, 47.56; H, 4.87; N, 4.14.

4-Methoxyphenylglycine (9)
Method A: Diethyl 2-amino-2-(4-methoxyphenyl)-malonate (**8d**, 563 mg, 2 mmol) and 6 N HCl (4 mL) were heated to reflux for 1 h. The solution was cooled at 0 °C for 1 h, the so formed crystals were isolated by filtration, triturated twice with Et_2O and dried under vacuum. The pure HCl salt of **9** was obtained as white crystals (347 mg, 80%). ^{1}H and ^{13}C NMR (DMSO-d_6) data matched previously published values.[19]

Method B: To a solution of diethyl 2-amino-2-(4-methoxyphenyl)-malonate (**8d**, 563 mg, 2 mmol) in THF (10 mL) was added aq 2 N LiOH (10 mL, 20 mmol). The mixture was vigorously stirred at r.t. for 2 h. The aqueous layer was washed with EtOAc (2 × 5 mL) and acidified with 1 N HCl until reaching pH 2. The solution was stirred at 50 °C for 15 min. The volume of the solution was reduced under vacuum to about 5 mL. The solution was cooled to 0 °C and the so formed white crystals were isolated by filtration to give the pure HCl salt of **9** (352 mg, 81%).

2-Thienylglycine (10)
Method A: Diethyl 2-amino-2-(2-thienyl)-malonate (**8e**, 586 mg, 2 mmol) and 6 N HCl (4 mL) were heated to reflux for 1 h. The solvent was removed in vacuo and the amino acid was purified by ion exchange. The HCl salt was dissolved in H_2O, and the pH adjusted to 7 by addition of 2 N NH_3. The solution was passed through a column with Amberlite IR-120 at the H^+ form eluting with 0.5 N NH_3. Removal of the solvents gave the ammonium salt which was dissolved in H_2O. The solution was passed through a column with Amberlite IR-420 at the OH^- form eluting with 0.5 N AcOH. Evaporation to dryness gave pure **10** as white crystals (264 mg, 84%); mp 204–210 °C (Lit.[20] mp 208–210 °C).

Method B: To a solution of diethyl 2-amino-2-(2-thienyl)-malonate (**8e**, 586 mg, 2 mmol) in THF (10 mL) was added aq 2 N LiOH (10 mL, 20 mmol). The mixture was vigorously stirred at r.t. for 2 h. The aqueous layer was washed with EtOAc (2 × 5 mL) and acidified with 1 N HCl until reaching pH 2. The solution was stirred at 50 °C for 15 min, the solvent removed under reduced pressure and the crude HCl salt purified by ion exchange. Pure **10** was obtained as white crystals (248 mg, 79%).

Acknowledgement

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