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New Selective Synthesis of Dimethyl 3-Alkylamino Itaconates

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Abstract: The ammonium **6** salt resulting from the reaction of the DABCO and the allyl bromide **2** was converted with good yields into a new family of dimethyl 3-amino itaconates **5**.

Keywords: Allyl amines, DABCO, dimethyl α-(bromomethyl) fumarate, dimethyl itaconates, regioselectivity

INTRODUCTION

The dimethyl α-(bromomethyl) fumarate **2**[1–4] is a required compound in organic synthesis. Indeed, it constitutes a key intermediary in the synthesis and the development of molecules with biological properties. Starting from commercially dimethyl itaconate **1**, the addition of bromine under reflux of carbon tetrachloride gives an intermediate dibromide compound that can be easily converted into a regio- and stereoselective[5] dehydrobromination process induced with triethylamine to give the dimethyl α-(bromomethyl) fumarate **2** in 73% overall yield (Scheme 1).

Previous reports have investigated factors that influence the reactivity of allylic systems with amines.[6–14] In this report, we found that

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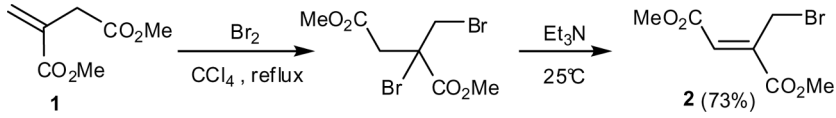
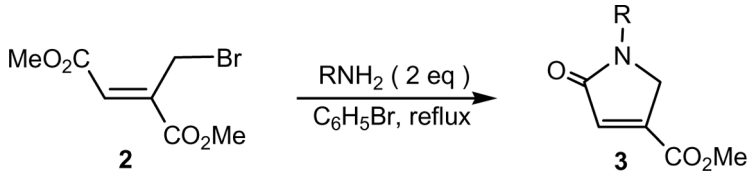


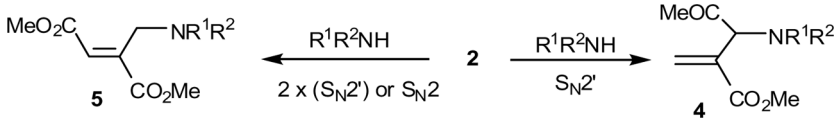
Scheme 1.

the allyl bromide **2** revealed a high synthetic potentiality induced by its easy conversion into different heterocyclic and aliphatic compounds. In fact, it opposed an increased reactivity with primary amines (2 eq.) in the bromobenzene at reflux, leading exclusively via two successive allylic substitutions ($2 \times S_N2'$) followed by an intermolecular cyclization to produce a new functional pyrrolin-2-ones **3**[15] with high yields (Scheme 2).

On the other hand, the treatment of **2** with excess secondary amines (2–4 molar equivalents) at 25 °C leads to the corresponding allyl amino substrates or S_N2' type-products **4**,[16–19] which deserve special attention as a result of their physiological properties,[20] biological activities,[21,22] and their presence in several natural products.[23,24] However, in less bulky or bulky secondary amines the secondary amines, allyl bromide **2**, can only be transformed into products **5** arising from two bimolecular S_N2' type-reactions (Scheme 3).



Scheme 2.

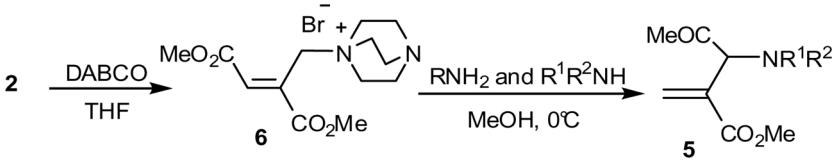


Scheme 3.

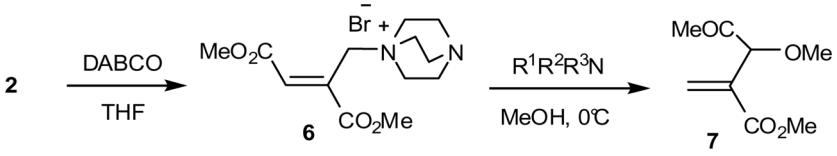
RESULTS AND DISCUSSION

In light of the results obtained, we propose a new strategy for the production of functional allylic amines **4** in high yields regardless of the size of the amine (primary, secondary, as well as tertiary amines) via the successive reaction coupling of functional allyl bromide **2** with diazabicyclo[2.2.2]octane (DABCO) for 3 h in tetrahydrofuran (THF) at 25 °C followed by the replacement of THF by methanol, then the addition of amine (1 molar equivalent) at low temperature (0 °C). As a bulky diamine, the nucleophilic substitution on the allylic bromide **2** by DABCO promotes first a S_N2' type-reaction, in a second step, the amine proceeds in a S_N2' process providing the liberation of the DABCO. Highly pure allyl amines **5** were obtained in good yields (Scheme 4). It should be noted that this method can be extended to the primary amines and some slightly bulky secondary amines.

Unexpectedly, an easy coupling between the formed salt **6** and some bulky secondary and tertiary amines such as diethylamine, diisopropylamine, diphenylamine, and triethylamine, led to only one functionalized allyl ether **7** resulting from S_N2' reaction of the methanol as solvent and nucleophilic reagent (Scheme 5). Because of the important steric hindrance, the conjugate addition of these amines was not observed, but the allylic ether formation was much faster in the presence of amine (1.8–3 h) than when the methanol was used only (1 week). As mentioned in the literature, conjugate reaction of nucleophilic reagent in protic solvent to activated olefins was pseudo second order and kinetically much faster.[25]



Scheme 4.



Scheme 5.

In summary, we have developed an efficient and simple regio- and stereoselective synthesis of functional allylamine via an effective coupling of primary, secondary amines, and dimethyl α-(bromomethyl) fumarate **2**.

EXPERIMENTAL

All reactions were monitored by thin-layer chromatography (TLC) on silica-gel plates (Fluka Kieselgel 60 F_{254}). For column chromatography, Fluka Kieselgel (70–230) mesh was used. ^{1}H and ^{13}C NMR (fully decoupled) and spectra were recorded on Bruker AMX 300 spectrometers in $CDCl_3$ as solvent and TMS as the internal. ^{1}H and ^{13}C NMR (fully decoupled) were recorded on Bruker AMX 300 in $CDCl_3$ as solvent and TMS as the internal standard. Mass spectrometry was performed on an Autospec 200, Micromass (Waters) instrument.

Synthesis of Dimethyl 3-Alkylamono Itaconates 5a–i: Typical Procedure

To 8.44 mmol (2 g) of dimethyl α-(bromomethyl) fumarate **2** in 30 ml of THF, 1.13 g (10.13 mmol) of DABCO were added under magnetic stirring during 3 h until the allyl bromide salt was formed. The solvent was removed in vacuum and the obtained residue was dissolved in 20 ml of methanol. The amine (8.44 mmol) diluted in 5 mL of methanol was added dropwise at 0 °C. After the completion of the reaction indicated by TLC analysis, the solvent was evaporated under reduced pressure and the crude mixture was purified by silica-gel flash chromatography (hexane/EtOAc, 80/20) to give the corresponding dimethyl 3-alkylamino itaconate **5**.

Table 1. Synthesis of dimethyl 3-alkylamino itaconates **5a–i**

5	R^1	R^2	Time (h)	Yield (%)
5a	H	Ph-CH_2	1	89
5b	H	Ph-(CH_3)-CH	1	87
5c	H	p-FC_6H_4-CH_2	0.5	85
5d	H	p-$MeOC_6H_4$-CH_2	0.3	78
5e	H	p-ClC_6H_4-CH_2	0.3	76
5f	H	^{n}Bu	0.5	72
5g	H	^{i}Pr	0.5	69
5h	H	$^{c}C_6H_{11}$	0.5	70
5i	Me	$^{c}C_6H_{11}$	0.5	79

Table 2. Synthesis of dimethyl 2-methoxy-3-itaconate **7**

Ether	R^1	R^2	R^3	Time (h)	Yield (%)
7	Et	Et	H	1,8	83
7	^{i}Pr	^{i}Pr	H	2	85
7	Ph	Ph	H	3	72
7	Et	Et	Et	3	70

Data

Dimethyl 3-Benzylamino Itaconate **5a**

^{1}H NMR ($CDCl_3$, δ ppm, *J* Hz): 7.27 (m, 5H); 6.34 (s, 1H), 5.79 (1 s, 1H), 4.17 (s, 1H), 3.79 (d, 2H, $J = 4.05$), 3.75 (s, 3H), 3.70 (s, 3H), 2.35 (br s, 1H). ^{13}C NMR ($CDCl_3$, δ ppm): 172.42 (*C*=O), 166.11 (*C*=O), 139.31 (=*C*), 137.72 (aromatique *C*), 128.42 (aromatique *C*H), 128.24 (aromatique *C*H), 127.74 (aromatique *C*H), 127.15 (=*C*H_2), 61.16 (*C*H), 52.33 (O*C*H_3), 52.08 (O*C*H_3), 51.42 (Ph−*C*H_2).

Dimethyl 3-(1-Phenylethylamino) Itaconate **5b**

^{1}H NMR ($CDCl_3$, δ ppm, *J* Hz): 7.28 (m, 5H); 6.25 (d, 1H, $J = 31.60$), 5.62 (d, 1H, $J = 10.29$), 3.96 (d, 1H, $J = 1.36$), 3.94 (q, 1H, $J = 7.23$), 3.72 (s, 3H), 3.67 (s, 3H), 2.33 (br s, 1H), 6.25 (d, 3H, $J = 6.60$). ^{13}C NMR ($CDCl_3$, δ ppm): 173.13 (*C*=O), 166.01 (*C*=O), 144.47 (=*C*), 138.75 (aromatic *C*), 128.33 (aromatic *C*H), 127.19 (aromatic *C*H), 127.02 (aromatic *C*H), 126.32 (=*C*H_2), 60.15 (O=C−*C*H), 56.85 (H_3C−*C*H), 52.17 (O*C*H_3), 51.90 (O*C*H_3), 24.42 (*C*H_3). HRMS calcd. for $C_{15}H_{19}NO_4$: 277.1314; found: 277.1314.

Dimethyl 3-(4-Fluorobenzylamino) Itaconate **5c**

^{1}H NMR($CDCl_3$, δ ppm, *J* Hz): 7.28 (dd, 2H, $J = 8.46$, $J = 8.46$), 6.99 (t, 2H, $J = 7.32$), 6.34 (s, 1H), 5.79 (1 s, 1H), 4.15 (s, 1H), 3.75 (s, 2H), 3.75 (s, 3H), 3.70 (s, 3H),2.35(br s, 1H). ^{13}C NMR ($CDCl_3$, δ ppm): 172.48 (*C*=O), 166.18 (*C*=O), 162.13 (d, aromatic *C*−F, $J^1 = 144.75$), 137.85 (=*C*), 135.19 (aromatic *C*−CH_2), 129.87, 129.97 (aromatic *C*H), 127.78 (=*C*H_2), 115.13, 115.41 (aromatic *C*H), 61.23 (*C*H−HN), 50.81, 52.43 (O*C*H_3), 52.19 (*C*H_2−Ph).

Dimethyl 3-(4-Methoxybenzylamino) Itaconate **5d**

^{1}H NMR ($CDCl_3$, δ ppm, *J* Hz): 7.13 (d, 2H, *J* = 4.09), 6.74 (d, 2H, *J* = 4.09), 6.24 (s, 1H), 5.69 (1 s, 1H), 4.06 (s, 1H), 3.66 (s, 3H), 3.65 (s, 3H), 3.62 (d, 2H, *J* = 4.41), 3.60 (s, 3H), 2.19 (br s, 1H). ^{13}C NMR ($CDCl_3$/TMS): 172.26 (*C*=O), 165.93 (*C*=O), 158.65 (aromatic *C*−OMe), 137.65 (=*C*), 131.23 (aromatic *C*H), 129.26 (aromatic *C*), 127.41 (=*C*H$_2$), 113.63 (aromatic *C*H), 60.82 (O=C−*C*H), 55.01 (Ph−O*C*H$_3$), 52.07 (O*C*H$_3$), 51.85 (O*C*H$_3$), 50.64 (Ph−*C*H$_2$).

Dimethyl 3-(4-Chlorobenzylamino) Itaconate **5e**

^{1}H NMR ($CDCl_3$, δ ppm): 7.29 (s, 4H), 6.35 (s, 1H), 5.81 (s, 1H), 4.13 (s, 1H), 3.81 (s, 2H), 3.75 (s, 3H), 3.71 (s, 3H), 2.41 (br s, 1H). ^{13}C NMR ($CDCl_3$, δ ppm): 171.76 (*C*=O), 166.26 (*C*=O), 137.45 (=*C*), 135.25 (aromatic *C*−CH$_2$), 131.23 (aromatic *C*–Cl), 129.26 (aromatic *C*H), 127.41 (aromatic *C*H), 121.63 (=*C*H$_2$), 61.62 (O=C−*C*H), 52.29 (O*C*H$_3$), 52.17 (O*C*H$_3$), 51.84 (Ph−*C*H$_2$).

Dimethyl 3-Butylamino Itaconate **5f**

^{1}H NMR ($CDCl_3$, δ ppm, *J* Hz): 6.34 (s, 1H), 5.83 (s, 1H), 4.18 (s, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 2.57 (m, 2H), 1.91 (br s, 1H), 1.43 (m, 2H), 1.37 (m, 2H), 0.90 (t, 3H, *J* = 6.99). ^{13}C NMR ($CDCl_3$, δ ppm): 172.25 (*C*=O), 165.82 (*C*=O), 137.70 (=*C*), 127.01 (=*C*H$_2$), 61.90 (O=C−*C*H), 51.92 (O*C*H$_3$), 51.72 (O*C*H$_3$), 47.33 (HN−*C*H$_2$), 31.73 (H$_2$C−*C*H$_2$), 20.05 (H$_3$C−*C*H$_2$), 13.57 (*C*H$_3$). HRMS calcd. for $C_{11}H_{19}NO_4$: 229.1316; found: 229.1314.

Dimethyl 3-Isopropylamino Itaconate **5g**

^{1}H NMR ($CDCl_3$, δ ppm, *J* Hz): 6.32 (s, 1H), 5.82 (s, 1H), 4.30 (s, 1H), 3.78 (d, 2H, *J* = 4.09), 3.77 (s, 3H), 3.72 (s, 3H), 2.79 (st, 1H, *J* = 6.24), 1.99 (br s, 1H), 1.06 (d, 6H, *J* = 6.24). ^{13}C NMR ($CDCl_3$, δ ppm): 173.05 (*C*=O), 166.18 (*C*=O), 138.58 (=*C*), 127.14 (=*C*H$_2$), 59.59 (O=C−*C*H), 52.32 (O*C*H$_3$), 52.08 (O*C*H$_3$), 46.69 (H$_3$C−H*C*−CH$_3$), 22.78 (*C*H$_3$).

Dimethyl 3-Cyclohexylamino Itaconate **5h**

^{1}H NMR ($CDCl_3$, δ ppm): 6.32 (s, 1H), 5.82 (s, 1H), 4.36 (s, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 2.40 (qt, 1H, *J* = 6.63), 2.40 (m, 1H), 1.94 (br s, 1H),

1.82 (m, 2H), 1.72 (m, 2H), 1.65 (m, 2H), 1.20 (m, 2H), 1.14 (m, 2H), 1.73 (m, 6H), 1.17 (m, 4H). ^{13}C NMR ($CDCl_3$/TMS): 173.16 (*C*=O), 166.22 (*C*=O), 138.66 (=*C*), 127.04 (=*C*H_2), 58.94 (O=C−*C*H), 54.79 (HN−*C*H), 52.39 (O*C*H_3), 54.32 (O*C*H_3), 33.36 (*C*H_2), 26.01 (*C*H), 24.83 (*C*H_2).

Dimethyl 3-N,N-Cyclohexylmethylamino Itaconate **5i**

^{1}H NMR ($CDCl_3$, δ ppm): 6.38 (s, 1H), 5.95 (s, 1H), 4.55 (s, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 2.57 (m, 1H), 2.32 (s, 3H), 1.70 (m, 6H), 1.30 (m, 4H). ^{13}C NMR ($CDCl_3$, δ ppm): 171.91 (*C*=O), 167.05 (*C*=O), 137.66 (=*C*), 126.68 (=*C*H_2), 63 (O=C−*C*H), 61.61 (N−*C*H), 52.19 (O*C*H_3), 51.94 (O*C*H_3), 33.53 (N−*C*H_3), 30.56 (CH_2), 30.15 (*C*H_2), 26.39 (*C*H). HRMS calcd. for $C_{14}H_{23}NO_4$: 269.1623; found: 269.1627.

Synthesis of Dimethyl 3-Methoxy Itaconate **7**: Genral Procedure

To 4.22 mmol (1 g) of dimethyl α-(bromomethyl) fumarate **2** in 15 ml of THF, 0.565 g (5.06 mmol) of DABCO was added under magnetic stirring during 3 h until the allyl bromide salt was formed. After removing THF, the obtained salt from the reaction coupling of the allyl bromide, and DABCO, addition of 20 ml of methanol, secondary, or tertiary amine (4.22 mmol) diluted in 2.5 mL of methanol was added dropwise at 0 °C. After the total formation of ether **7** (TLC analysis), the excess of the solvent was evaporated under reduced pressure and the crude mixture was purified by silica-gel flash chromatography (hexane/EtOAc, 80/20) to give the corresponding dimethyl 3-methoxy itaconate **7**.

^{1}H NMR ($CDCl_3$, δ ppm): 6.49 (s, 1H), 6.01 (s, 1H), 4.71 (s, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.46 (s, 3H). ^{13}C NMR ($CDCl_3$/TMS): 170.18 (*C*=O), 165.57 (*C*=O), 136.25 (=*C*), 128.52 (=*C*H_2), 78.74 (O=C−*C*H), 58.20 (HC−O*C*H_3), 52.42 (O*C*H_3), 52.24 (O*C*H_3). HRMS calcd. For $C_8H_{12}O_5$: 188.0686; found: 188.0685.

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