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Iminomalonate as a Convenient Electrophilic Amination Reagent for Grignard Reagents

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Diethyl 2-[*N*-(*p*-methoxyphenyl)imino]malonate underwent amination reactions with alkyl Grignard reagents to give *N*-aklylation products in good yields. The obtained *N*-alkylation products were readily converted into *N*-alkyl-*p*-anisidines by the oxidative removal of the malonate moiety. The *p*-methoxyphenyl group was subsequently deprotected to give primary amines.

Electrophilic amination is a useful method for C–N bond formation, and several reagents including azodicarboxylates have been developed for this purpose.[1,2] Recently, new reagents, such as oxaziridines,[3] oximes,[4] and oxime *O*-sulfonates,[5] have also been developed as electrophilic amination reagents. However, because amination reactions using these reagents were not always readily carried out, the development of a new electrophilic amination reagent has been highly desirable. On the other hand, some *N*-alkylation reactions to α-imino esters have been known.[6] In particular, the Grignard reagent is one of the most convenient *N*-alkylation reagents for α-imino esters. In our laboratory, we recently described the coupling reactions of α-iminoacetates with dialkylaluminum chloride to give *N*-monoalkylated 1,2-diamines in good yields.[7] During these studies we found that imines with two electron-withdrawing substituents possessed good abilities to react with nucleophiles on the nitrogen atom in a regioselective manner. We studied these reactions in detail, and wish to report that 2-[*N*-(*p*-methoxyphenyl)imino]malonate is an efficient reagent for the electrophilic amination of Grignard reagents to give *N*-alkylation products and that the subsequent oxidation of the malonate moiety affords *N*-alkyl-*p*-anisidines in good yields.[8]

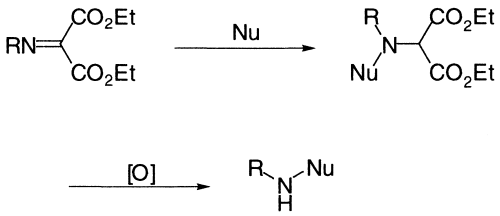
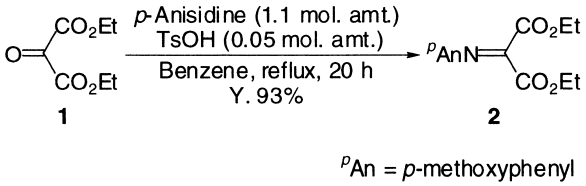


Chart 1.



Scheme 1. Preparation of iminomalonate.

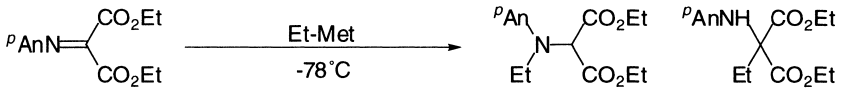
Results and Discussion

The following sequence shows the present strategy (Chart 1). The new electrophilic amination methodology consists of two reactions: 1) a nucleophilic addition to the nitrogen atom, and 2) an oxidative removal of the malonate moiety. Among various imine derivatives possessing electron-withdrawing groups, iminomalonate was chosen as an amination reagent. Several iminomalonates have already been known and used for the synthesis of heterocycles.[9,10] However, the nucleophilic addition of organometals to this imine has not received much attention. Due to a ready removal from the nitrogen atom after the additon of nucleophiles, the *p*-methoxyphenyl group was chosen as a substituent at the nitrogen.

An amination reagent, diethyl 2-[*N*-(*p*-methoxyphenyl)imino]malonate (**2**),[10] was easily prepared by the condensation of commercially available diethyl 2-oxomalonate (**1**)[11] with *p*-anisidine in 93% yield (Scheme 1):

To perform electrophilic amination, we screened the most effective organometal. The ethylation of the imine **2** with several organometals was examined as a model. As shown in Table 1, diethylaluminum chloride showed a good tendency for *N*-ethylation to give the desired **3a** in 66% yield (entry 2), whereas triethylborane afforded only the *C*-ethylation product (entry 4). In a toluene solution, diethyl zinc gave *N*-ethylated product **3a** in 80% yield along with a *C*-ethylation product **4a** (entry 6). *N*-Ethylation product **3a** was obtained in 84% yield using ethylmagnesium bromide (entry 7). From the above results and the accessibility of nucleophiles, Grignard reagents were chosen as nucleophiles. After an investigation into the solvent effects and the molar amounts of the Grignard reagent, 1.5 molar amounts of ethylmagnesium bromide in THF was found to be the most effective to give the *N*-ethylation product **3a** in 91% yield (entry 10). In each case, the yield was determined by ^{1}H-NMR based on the relative intensity of the methine proton to that of pyrazine as an internal standard because

Table 1. Ethylation of Iminomalonate **2** Using Several Organometals

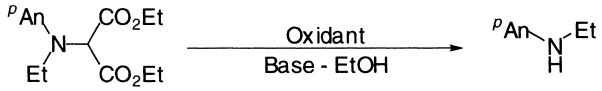


2 **3a** **4a**

Entry	Et-Met (mol amt.)	Solvent	Time/min	Yield of **3a**/% [a]	Yield of **4a**/% [a]
1	$EtAlCl_2$ (3.0)	CH_2Cl_2	65	32	—
2	Et_2AlCl (3.0)	CH_2Cl_2	18	66	—
3	Et_3Al (3.0)	CH_2Cl_2	42	25	24
4	Et_3B (3.0)	Toluene	27 h [b]	—	39
5	Et_2Zn (3.0)	THF	56	40	23
6	Et_2Zn (3.0)	Toluene	17	80	15
7	EtMgBr (1.2)	THF	60	84	—
8	EtMgBr (1.2)	Et_2O	10	59	—
9	EtMgBr (1.2)	Toluene	17	50	—
10	EtMgBr (1.5)	THF	30	91	—

a) Yields were determined by ^{1}H NMR using pyrazine as an internal standard. b) Reaction was carried out at –78 °C to reflux temperature.

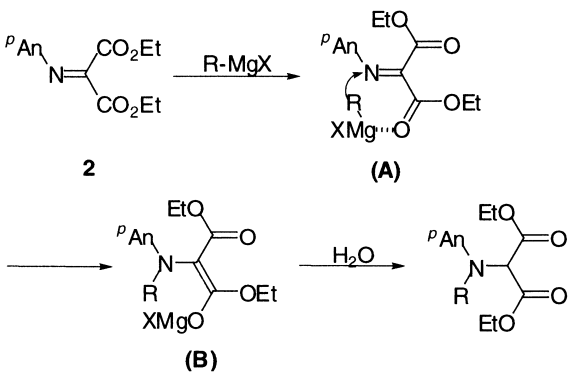
Table 2. Oxidative Cleavage of *N*-Ethylation Product **3a**



3a **5a**

Entry	Oxidant (mol amt.)	Base	Temp/°C	Time/h	Yield/% [a]
1	$PhI(OAc)_2$ (1.5)	KOH (2 M) [b]	0 ~ rt	17.0	22
2	$PhI(OAc)_2$ (1.5)	KOH (2 M) [b]	0 ~ 80	17.0	22
3	$PhI(OTfa)_2$ (1.5)	KOH (2 M) [b]	0 ~ rt	26.0	54
4	PhIO (1.5)	KOH (2 M) [b]	0 ~ rt	22.0	82
5	Air	KOHaq (0.44 mol. amt.)	rt	48.0	57
6	Air	KOHaq (0.44 mol. amt.)	50	43.5	21
7	Air [c]	KOHaq (0.44 mol. amt.)	rt	48.0	93
8	Air [c]	KOHaq (0.88 mol. amt.)	rt	37.5	54
9	O_2	KOHaq (0.44 mol. amt.)	rt	22.5	45

a) Isolated yields. b) 1 M = 1 mol dm^{-3} c) Worked up with 10% aqueous Na_2SO_3.



2 **(A)** **(B)**

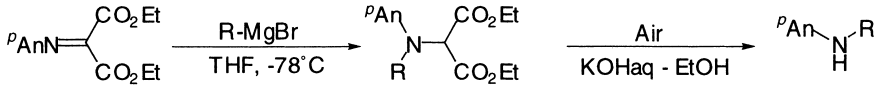
Scheme 2. Mechanism of the amination reaction.

of the instability of *N*-ethylation product **3a**. Although the *N*-ethylation product **3a** could not be always isolated, careful purification enabled the isolation of **3a**, which was determined by the LC-MS, ^{1}H-NMR and IR spectra.

A plausible mechanism of this amination reaction is shown in Scheme 2.[6a] The magnesium of the Grignard reagent initially coordinates to the ester carbonyl group of iminomalonate **2**, making the electron density of the nitrogen atom decrease; alkyl group then attacks the nitrogen atom (**A**) to afford the magnesium enolate (**B**), which in turn is hydrolyzed to give an *N*-alkylation product (Scheme 2):

In order to obtain *N*-ethyl-*p*-anisidine (**5a**), the oxidative removal of the malonate moiety was next examined (Table 2). It is required to use an oxidant that induces α-hydroxylation of a carbonyl compound, where the nitrogen moiety should be intact. The use of (diacetoxyiodo)benzene was firstly attempted.[12] However, *N*-ethyl-*p*-anisidine (**5a**) was obtained in only 22% yield (entries 1 & 2). Iodosylbenzene was proved to be an effective oxidant for this reaction to give the desired product **5a** in 82% yield (entry 4).[13] Because oxidation with air is a more inexpensive and convenient method,[14] air oxidation was next examined (entries 5–8). In this case, *N*-ethyl-*p*-anisidine (**5a**) was obtained in 57% yield (entry 5). The yield was improved up to 93% by treating with 10% aqueous Na_2SO_3 for the work-up procedure (entry 7). In contrast, oxygen was not

Table 3. Synthesis of *N*-Alkyl-*p*-anisidine by Electrophilic Amination



2 **3** **5**

Entry	R	Products	Yield of **3**/%[a), b)]	Yield of **5**/%[c)]
1	Methyl	**3b, 5b**	98	63
2	Ethyl	**3a, 5a**	91	93
3	Propyl	**3c, 5c**	81	79
4	Butyl	**3d, 5d**	98 (60)[d)]	92
5	Decyl	**3e, 5e**	78	79
6	Dodecyl	**3f, 5f**	94	84
7	Tetradecyl	**3g, 5g**	79	71
8	Phenethyl	**3h, 5h**	86	89
9	Cyclohexylmethyl	**3i, 5i**	93	91
10[e), f)]	Isopropyl	**3j, 5j**	86	57[g)]
11[e)]	Cyclohexyl	**3k, 5k**	48	29[g)]
12[e)]	Benzyl	**3l, 5l**	80	64[g)]
13[e)]	Phenyl	**3m, 5m**	59	55[g)]
14[e)]	*tert*-Butyl	**3n, 5n**	56[c)]	67[h)]

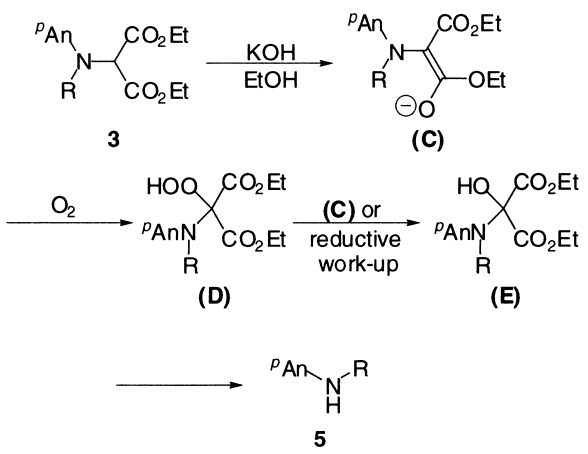
a) Yields were determined by ^{1}H NMR using pyrazine as internal standard. b) ^{1}H-NMR spectra of compounds **3** taken in $CDCl_3$ showed no enol proton. c) Isolated yields. d) In the parenthesis, butylmagnesium bromide was prepared from butyllithium and $MgBr_2$. e) Carried out at −95 °C. f) When first step was carried out at −78 °C, *N*-isopropyl-*p*-anisidine (**5j**) was obtained in 23%. g) Overall yield from **2**. h) Oxidative cleavage was performed with iodosylbenzene.

the reagent of choice in terms of the product yield, although the reaction time was shortened (entry 9). The low yield may be caused by over-oxidation of the obtained amine **5a**.

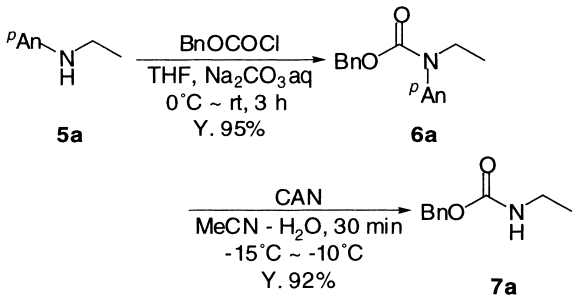
The mechanism of this oxidative removal with air is shown below (Scheme 3). The α-proton of the *N*-alkylation product **3** is deprotonated under basic conditions. The formed enolate (**C**) is then oxidized to give the intermidiate (**D**). This hydroperoxide (**D**) is attacked by another enolate (**C**), or reduced during the work-up to form the hemiaminal (**E**); a subsequent elimimation reaction gives *N*-alkyl-*p*-anisidine **5**.

Next, the amination reaction was examined using a variety of Grignard reagents followed by oxidative cleavage. The results are summarized in Table 3. Electrophilic amination using primary alkyl Grignard reagents afforded the desired products in good-to-excellent yields. Subsequent oxidative cleavage of the *N*-alkylated products also proceeded smoothly to give *N*-alkyl-*p*-anisidines. In entry 4, *N*-alkylation reaction was also examined with Grignard reagent prepared from butyllithium and $MgBr_2$. In this case, the reaction proceeded similarly. Various alkylations including secondary or tertiary alkyl and aryl Grignard reagent could be carried out (entries 10–14). In entries 10–13, an α-proton of the crude products **3** was clearly identified in ^{1}H NMR. However, other portions of the ^{1}H NMR spectra were not clear due to by-products and, therefore, the overall yields of **5** from the imine **2** are shown. Although isopropylation was conducted, *N*-isopropyl-*p*-anisidine (**5j**) was obtained in 23% yield. This lower yield may be due to the inefficiency of addition caused by the steric bulk of the Grignard reagent. To improve the yield of *N*-isopropyl-*p*-anisidine (**5j**), various conditions were examined. When the reaction was carried out at −95 °C, the yield was improved to 57% (entry 10). However, additives such as CuI, $BF_3{\cdot}OEt_2$, $CeCl_3$, and $MgBr_2$ were not effective. The *N*-methylation and *tert*-butylation of α-iminoacetate were reported to be highly difficult.[6a] In strong contrast to the previous observations, due to the introduction of two ester groups into the imino carbon, the present amination tolerates wide range or Grignard reagents, and shows high regioselectivity onto the nitrogen atom for the nucleophilic addition.

The *p*-methoxyphenyl moiety of *N*-alkyl-*p*-anisidine was readily deprotected with ammonium cerium(IV) nitrate to give a primary amine (Scheme 4).[15] *N*-Ethyl-*p*-anisidine (**5a**) was



Scheme 3. Mechanism of the oxidative cleavage.



Scheme 4. Removal of *p*-methoxyphenyl group.

firstly converted into benzylcarbamate **6a** with benzyl chloroformate in 95% yield.[16] This carbamate was exposed to CAN in the usual manner to give benzyl *N*-ethylcarbamate (**7a**) in 92% yield.

Conclusion

Iminomalonate was found to be an efficient electrophilic amination reagent for Grignard reagents. In particular, diethyl 2-[*N*-(*p*-methoxyphenyl)imino]malonate was proved to be the most efficient amination reagent for primary alkyl Grignard reagents to give *N*-alkyl-*p*-anisidines in excellent yields, although electrophillic amination of secondary, tertiary-alkyl and aryl Grignard reagents gave slightly lower yields of the amination products. In view of preparing the iminomalonate and removing the *p*-methoxyphenyl moiety, this method is a useful addition to the existing methodologies for electrophilic amination.

Experimental

General Aspects. Infrared spectra were determined on a JASCO IR-810 spectrometer. ^{1}H NMR and ^{13}C-NMR spectra were recorded with a JEOL EX-270 or a JEOL α-500 spectrometer using tetramethylsilane as an internal standard. HRMS were determined with a JEOL JMX-AX505HA. THF and ether were distilled from sodium diphenylketyl before use. Ethanol was distilled from sodium ethoxide. Preparative TLC purification was carried out using silica gel (Merck Kiesel Gel PF254).

Diethyl 2-[*N*-(*p*-Methoxyphenyl)imino]malonate (2):[10] To a solution of *p*-anisidine (812.9 mg, 6.6 mmol) in benzene (30 mL) were added diethyl 2-oxomalonate (0.963 mL, 6.0 mmol) and *p*-toluenesulfonic acid (57.1 mg, 0.3 mmol) under an argon atmosphere. The reaction mixture was heated at reflux for 20 h with azeotropic removal. The solvent was evaporated, and the residue was purified with Kugelrohr distillation to give the title product in 93% yield (bp 138 °C/43 Pa). ^{1}H NMR ($CDCl_3$) δ 1.18 (t, J = 7.3 Hz, 3H), 1.40 (t, J = 7.3 Hz, 3H), 3.81 (s, 3H), 4.25 (q, J = 7.3 Hz, 2H), 4.44 (q, J = 7.3 Hz, 2H), 6.88 (d, J = 8.9 Hz, 2H), 7.08 (d, J = 8.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.78, 14.05, 55.40, 62.03, 62.79, 114.20, 122.59, 140.20, 150.18, 159.23, 161.33, 163.40; IR (neat) 2950, 1750, 1510, 1260, 1080, 860 cm^{-1}.

Diethyl 2-[Ethyl(*p*-methoxyphenyl)amino]malonate (3a): Under an argon atmosphere, to a solution of diethyl 2-[*N*-(*p*-methoxyphenyl)imino]malonate (83.8 mg, 0.300 mmol) in THF (5.00 mL), EtMgBr (0.542 mL, 0.450 mmol, 0.83 M in THF) was slowly added at −78 °C. After 30 min, saturated aqueous $NaHCO_3$ was added, and the whole mixture was then extracted with ethyl acetate (10 mL × 3). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The yield was determined by ^{1}H NMR using pyrazine as an internal standard to indicate the formation of diethyl 2-[ethyl(*p*-methoxyphenyl)amino]malonate in 91%. ^{1}H NMR ($CDCl_3$) δ 1.12 (t, J = 7.3 Hz, 3H), 1.27 (t, J = 7.3 Hz, 6H), 3.44 (q, J = 7.3 Hz, 2H), 3.76 (s, 3H), 4.24 (q, J = 7.3 Hz, 4H), 4.88 (s, 1H), 6.76–6.88 (m, 4H); IR (neat) 2950, 1760, 1620, 1520, 1260, 1040, 830, 760, 660, 570 cm^{-1}. LC-MS (ESI) m/z 310 (M + H)$^+$.

Diethyl 2-Ethyl-2-[(*p*-methoxyphenyl)amino]malonate (4a): ^{1}H NMR ($CDCl_3$) δ 0.77 (t, J = 7.6 Hz, 3H), 1.21 (t, J = 7.3 Hz, 6H), 2.29 (q, J = 7.6 Hz, 2H), 3.73 (s, 3H), 4.22 (q, J = 7.3 Hz, 4H), 4.81 (s, 1H), 6.61 (d, J = 8.9 Hz, 2H), 6.73 (d, J = 8.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 7.43, 13.98, 24.52, 55.56, 62.06, 69.14, 114.62, 116.86, 137.92, 152.92, 170.21; IR (neat) 3380, 2950, 1740, 1520, 1250, 1040, 830 cm^{-1}. HRMS m/z calcd for $C_{16}H_{23}NO_5$ (M$^+$): 309.1576, found: 309.1561.

Diethyl 2-[(*p*-Methoxyphenyl)methylamino]malonate (3b): ^{1}H NMR ($CDCl_3$) δ 1.28 (t, J = 7.3 Hz, 6H) 3.02 (s, 3H), 3.75 (s, 3H), 4.25 (q, J = 7.3 Hz, 4H), 4.98 (s, 1H), 6.72–6.91 (m, 4H); IR (neat) 3350, 2920, 1520, 1240, 1050, 830 cm^{-1}.

Diethyl 2-[(*p*-Methoxyphenyl)propylamino]malonate (3c): ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 7.3 Hz, 3H), 1.27 (t, J = 7.3 Hz, 6H), 1.46–1.60 (m, 2H), 3.31 (t, J = 7.3 Hz, 2H), 3.76 (s, 3H), 4.23 (q, J = 7.3 Hz, 4H), 4.87 (s, 1H), 6.81 (d, J = 9.6 Hz, 2H). 6.88 (d, J = 9.6 Hz, 2H); IR (neat) 3350, 2920, 1520, 1240, 1050, 830 cm^{-1}.

Diethyl 2-[Butyl(*p*-methoxyphenyl)amino]malonate (3d): ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 3H), 1.21–1.37 (m, 2H), 1.27 (t, J = 7.3 Hz, 6H), 1.40–1.54 (m, 2H), 3.35 (t, J = 7.6 Hz, 2H), 3.76 (s, 3H), 4.23 (q, J = 7.3 Hz, 4H), 4.86 (s, 1H), 6.81 (d, J = 9.6 Hz, 2H), 6.88 (d, J = 9.6 Hz, 2H); IR (neat) 3370, 2950, 1530, 1250, 1060, 840 cm^{-1}.

Diethyl 2-[Decyl(*p*-methoxyphenyl)amino]malonate (3e): ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 6.9 Hz, 3H), 1.18–1.34 (m, 20H), 1.47–1.50 (m, 2H), 3.33 (t, J = 7.3 Hz, 2H), 3.76 (s, 3H), 4.23 (q, J = 7.3 Hz, 4H), 4.86 (s, 1H), 6.81 (d, J = 9.2 Hz, 2H), 6.87 (d, J = 9.2 Hz, 2H); IR (neat) 3350, 2900, 2840, 1750, 1530, 1480, 1250, 1190, 1050, 830 cm^{-1}.

Diethyl 2-[Dodecyl(*p*-methoxyphenyl)amino]malonate (3f): ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 6.9 Hz, 3H), 1.18–1.30 (m, 24H), 1.48–1.50 (m, 2H), 3.33 (t, J = 7.3 Hz, 2H), 3.76 (s, 3H), 4.23 (q, J = 7.3 Hz, 4H), 4.86 (s, 1H), 6.81 (d, J = 9.6 Hz, 2H), 6.87 (d, J = 9.6 Hz, 2H); IR (neat) 2900, 1750, 1530, 1480, 1260, 1180, 1050, 840 cm^{-1}.

Diethyl 2-[(*p*-Methoxyphenyl)tetradecylamino]malonate (3g): ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, J = 6.6 Hz, 3H), 1.26–1.30 (m, 28H), 1.50 (br, 2H), 3.34 (t, J = 7.9 Hz, 2H), 3.76 (s, 3H), 4.23 (q, J = 7.3 Hz, 4H), 4.86 (s, 1H), 6.81 (d, J = 9.2 Hz, 2H), 6.87 (d, J = 9.2 Hz, 2H). IR (neat) 2900, 1750, 1530, 1480, 1260, 1180, 1050, 840 cm^{-1}.

Diethyl 2-[(*p*-Methoxyphenyl)phenethylamino]malonate (3h): ^{1}H NMR ($CDCl_3$) δ 1.26 (t, J = 6.9 Hz, 6H), 2.81 (t, J = 7.3 Hz, 2H), 3.62 (t, J = 7.3 Hz, 2H), 3.78 (s, 3H), 4.19 (q, J = 6.9 Hz, 4H), 4.89 (s, 1H), 6.85 (d, J = 7.9 Hz, 2H), 6.95 (d, J = 7.9 Hz, 2H), 7.16–7.31 (m, 5H).

Diethyl 2-[Cyclohexylmethyl(*p*-methoxyphenyl)amino]malonate (3i): ^{1}H NMR ($CDCl_3$) δ 0.85–0.89 (m, 2H), 1.05–1.24 (m, 3H), 1.26 (t, J = 7.3 Hz, 6H), 1.38–1.46 (m, 1H), 1.59–1.77 (m, 5H), 3.20 (d, J = 7.3 Hz, 2H), 3.75 (s, 3H), 4.19–4.26 (m, 4H), 4.80 (s, 1H), 6.81 (d, J = 9.2 Hz, 2H), 6.98 (d, J = 9.2 Hz, 2H).

Diethyl 2-[*tert*-Butyl(*p*-methoxyphenyl)amino]malonate

(3n): ^{1}H NMR ($CDCl_3$) δ 1.07 (t, J = 7.3 Hz, 6H), 1.12 (s, 9H), 3.69 (s, 3H), 3.99 (q, J = 7.3 Hz, 4H), 4.77 (s, 1H), 6.66 (d, J = 8.6 Hz, 2H), 7.27 (d, J = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.88, 29.60, 55.18, 56.18, 61.05, 65.48, 112.78, 133.35, 137.61, 157.37, 169.88; IR (neat) 2950, 1760, 1620, 1520, 1475, 1380, 1055, 855 cm^{-1}. HRMS *m/z*: calcd for $C_{18}H_{27}NO_5$ (M^+): 337.1889, found: 337.1888.

***N*-Ethyl-*p*-anisidine (5a):** The crude product, including diethyl 2-[ethyl(*p*-methoxyphenyl)amino]malonate (0.274 mmol), was vigorously stirred in a mixture of 1.0 M KOHaq (0.121 mL) and EtOH (3.48 mL). After 48 h, 10% Na_2SO_3aq was added to this mixture. EtOH was then evaporated, and the residue was extracted with ethyl acetate (10 mL × 3). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by preparative TLC on silica gel (ethyl acetate/hexane =1:10) to give *N*-ethyl-*p*-anisidine (38.5 mg, 93%). ^{1}H NMR ($CDCl_3$) δ 1.24 (t, J = 7.3 Hz, 3H), 3.11 (q, J = 7.3 Hz, 2H), 3.74 (s, 3H), 6.59 (d, J = 8.9 Hz, 2H), 6.78 (d, J = 8.9 Hz, 2H), The N-H proton could not be detected; ^{13}C NMR ($CDCl_3$) δ 14.95, 39.48, 55.80, 114.14, 114.89, 142.68, 152.09; IR (neat) 2880, 1530, 1260, 1050, 830 cm^{-1}. HRMS *m/z*: Calcd for $C_9H_{13}NO$ (M^+): 151.0997, found: 151.0981.

***N*-Methyl-*p*-anisidine (5b):**[17] ^{1}H NMR ($CDCl_3$) δ 2.80 (s, 3H), 3.75 (s, 3H), 6.60 (d, J = 8.2 Hz, 2H), 6.80 (d, J = 8.2 Hz, 2H), The N-H proton could not be detected; ^{13}C NMR ($CDCl_3$) δ 31.66, 55.84, 113.73, 114.90, 143.54, 152.16; IR (neat) 3360, 2930, 1530, 1250, 830, 420 cm^{-1}.

***N*-Propyl-*p*-anisidine (5c):** ^{1}H NMR ($CDCl_3$) δ 0.99 (t, J = 7.3 Hz, 3H), 1.56–1.69 (m, 2H), 3.03 (t, J = 7.3 Hz, 2H), 3.75 (s, 3H), 6.58 (d, J = 9.2 Hz, 2H), 6.78 (d, J = 9.2 Hz, 2H), The N-H proton could not be detected; ^{13}C NMR ($CDCl_3$) δ 11.62, 13.98, 22.80, 46.84, 55.83, 114.03, 114.90, 142.81, 151.97; IR (neat) 3350, 2920, 1530, 1240, 1050, 830 cm^{-1}. HRMS *m/z*: calcd for $C_{10}H_{15}NO$ (M^+): 165.1154, found: 165.1145.

***N*-Butyl-*p*-anisidine (5d):**[17] ^{1}H NMR ($CDCl_3$) δ 0.95 (t, J = 7.3 Hz, 3H), 1.35–1.49 (m, 2H), 1.54–1.64 (m, 2H), 3.07 (t, J = 6.9 Hz, 2H), 3.75 (s, 3H), 6.59 (d, J = 8.9 Hz, 2H), 6.78 (d, J = 8.9 Hz, 2H), The N-H proton could not be detected; ^{13}C NMR ($CDCl_3$) δ 13.89, 20.29, 31.74, 44.73, 55.79, 114.05, 114.88, 142.76, 151.99; IR (neat) 3370, 2940, 1530, 1250, 1060, 830 cm^{-1}.

***N*-Decyl-*p*-anisidine (5e):** ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 6.9 Hz, 3H), 1.27–1.37 (m, 14H), 1.54–1.64 (m, 2H), 3.05 (t, J = 7.3 Hz, 2H), 3.74 (s, 3H), 6.57 (d, J = 8.9 Hz, 2H), 6.78 (d, J = 8.9 Hz, 2H), The N-H proton could not be detected; ^{13}C NMR ($CDCl_3$) δ 14.08, 22.65, 27.19, 29.30, 29.46, 29.55, 29.59, 29.68, 31.87, 45.04, 55.80, 114.01, 114.89, 142.85, 151.95; IR (neat) 3400, 2820, 1610, 1530, 1480, 1250, 1050, 830 cm^{-1}. HRMS *m/z*: calcd for $C_{17}H_{29}NO$ (M^+): 263.2249, found: 263.2239.

***N*-Dodecyl-*p*-anisidine (5f):** ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 6.9 Hz, 3H), 1.18–1.37 (m, 18H), 1.54–1.61 (m, 2H), 3.05 (t, J = 7.3 Hz, 2H), 3.74 (s, 3H), 6.57 (d, J = 8.9 Hz, 2H), 6.78 (d, J = 8.9 Hz, 2H), The N-H proton could not be detected; ^{13}C NMR ($CDCl_3$) δ 14.10, 22.68, 27.19, 29.33, 29.47, 29.60, 29.62, 29.65, 29.68, 31.91, 45.07, 55.83, 114.05, 114.90, 142.82, 151.99; IR ($CHCl_3$) 3400, 2900, 2820, 1520, 1475, 1300, 1260, 1050, 850 cm^{-1}. HRMS *m/z*: calcd for $C_{19}H_{33}NO$ (M^+): 291.2562, found: 291.2548.

***N*-Tetradecyl-*p*-anisidine (5g):** ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 3H), 1.14–1.37 (m, 22H), 1.54–1.64 (m, 2H), 3.05 (t, J = 6.9 Hz, 2H), 3.75 (s, 3H), 6.57 (d, J = 8.9 Hz, 2H), 6.78 (d, J = 8.9 Hz, 2H), The N-H proton could not be detected; ^{13}C NMR ($CDCl_3$) δ 14.09, 22.67, 27.19, 29.34, 29.46, 29.59, 29.65, 29.67, 29.69, 31.91, 45.03, 55.81, 114.00, 114.89, 142.87, 151.95; IR ($CHCl_3$) 3400, 2820, 1610, 1520, 1475, 1320, 1260, 1050, 850 cm^{-1}. HRMS *m/z*: calcd for $C_{21}H_{37}NO$ (M^+): 319.2875, found: 319.2846.

***N*-Phenethyl-*p*-anisidine (5h):**[18] ^{1}H NMR ($CDCl_3$) δ 2.90 (t, J = 6.9 Hz, 2H), 3.35 (t, J = 6.9 Hz, 2H), 3.74 (s, 3H), 6.58 (d, J = 8.9 Hz, 2H), 6.78 (d, J = 8.9 Hz, 2H), 7.20–7.34 (m, 5H), The N-H proton could not be detected; ^{13}C NMR ($CDCl_3$) δ 35.58, 46.04, 55.78, 114.38, 114.92, 126.35, 128.31, 128.56, 128.77, 139.38, 142.21, 152.18; IR (neat) 3360, 3000, 2900, 2800, 1520, 1250, 1050, 830, 750, 710 cm^{-1}.

***N*-Cyclohexylmethyl-*p*-anisidine (5i):** ^{1}H NMR ($CDCl_3$) δ 0.91–1.07 (m, 2H), 1.10–1.37 (m, 3H), 1.45–1.83 (m, 6H), 2.90 (d, J = 6.6 Hz, 2H), 3.22 (br, 1H), 3.74 (s, 3H), 6.56 (d, J = 8.9 Hz, 2H), 6.77 (d, J = 8.9 Hz, 2H), The N-H proton could not be detected; ^{13}C NMR ($CDCl_3$) δ 25.95, 26.57, 31.29, 37.57, 51.63, 55.79, 62.03, 113.88, 114.89, 142.92, 151.80; IR (neat) 3360, 2910, 2820, 1530, 1270, 1250, 1050, 830 cm^{-1}. HRMS *m/z*: calcd for $C_{14}H_{21}NO$ (M^+): 219.1623, found: 291.1634.

***N*-Isopropyl-*p*-anisidine (5j):**[2g] Under an argon atmosphere, to a solution of diethyl 2-[*N*-(*p*-methoxyphenyl)imino]malonate (83.8 mg, 0.300 mmol) in THF (5.00 mL), isopropylmagnesium bromide (0.542 mL, 0.450 mmol, 0.83 M in THF) was slowly added at –95 °C. After 30 min, saturated aqueous $NaHCO_3$ was added, and the whole mixture was then extracted with ethyl acetate (10 mL × 3). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Then, the crude product was vigorously stirred in a mixture of 1.0 M KOHaq (0.114 mL) and EtOH (3.30 mL). After 48 h, 10% Na_2SO_3aq was added to this mixture. EtOH was then evaporated, and the residue was extracted with ethyl acetate (10 mL × 3). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by preparative TLC on silica gel (ethyl acetate/hexane =1:15, twice) to give *N*-isopropyl-*p*-anisidine (28.2 mg, 57%). ^{1}H NMR ($CDCl_3$) δ 1.19 (d, J = 6.3 Hz, 6H), 3.48–3.61 (m, 1H), 3.74 (s, 3H), 6.57 (d, J = 8.9 Hz, 2H), 6.77 (d, J = 8.9 Hz, 2H), The N-H proton could not be detected; ^{13}C NMR ($CDCl_3$) δ 23.07, 45.24, 55.79, 114.93, 141.73, 151.95; IR (neat) 3350, 2940, 1525, 1470, 1240, 1180, 1050, 830, 760, 530 cm^{-1}.

***N*-Cyclohexyl-*p*-anisidine (5k):** The reaction was carried out as in the case with **5j** using cyclohexylmagnesium bromide (0.662 mL, 0.450 mmol, 0.68 M in THF), and *N*-cyclohexyl-*p*-anisidine (18.2 mg, 29%) was obtained. ^{1}H NMR ($CDCl_3$) δ 1.04–1.43 (m, 5H), 1.61–1.79 (m, 3H), 2.01–2.06 (m, 2H), 3.10–3.21 (m, 1H), 3.74 (s, 3H), 6.57 (d, J = 8.6 Hz, 2H), 6.76 (d, J = 8.6 Hz, 2H), The N-H proton could not be detected; ^{13}C NMR ($CDCl_3$) δ 14.09, 15.25, 22.63, 25.06, 25.97, 31.57, 33.60, 52.84, 55.81, 65.83, 114.89, 114.91, 141.53, 151.91; IR ($CHCl_3$) 3390, 2970, 2910, 2830, 1520, 1460, 1300, 1250, 830 cm^{-1}. HRMS *m/z*: calcd for $C_{13}H_{19}NO$ (M^+) 205.1467, found 205.1470.

***N*-Benzyl-*p*-anisidine (5l):**[17] The reaction was carried out as in the case with **5j** using benzylmagnesium chloride (1.17 mL, 0.450 mmol, 0.39 M in THF), and *N*-benzyl-*p*-anisidine (40.8 mg, 64%) was obtained. ^{1}H NMR ($CDCl_3$) δ 3.74 (s, 3H), 4.28 (s, 2H), 6.60 (d, J = 8.9 Hz, 2H), 6.77 (d, J = 8.9 Hz, 2H), 7.24–7.38 (m, 5H), The N-H proton could not be detected; ^{13}C NMR ($CDCl_3$) δ 49.31, 55.79, 114.21, 114.90, 127.17, 127.56, 128.57, 139.57, 142.29, 152.27; IR (neat) 3400, 2820, 1530, 1260, 840 cm^{-1}.

***N*-Phenyl-*p*-anisidine (5m):**[19] The reaction was carried out as in the case with **5j** using phenylmagnesium bromide (0.616 mL, 0.450 mmol, 0.73 M in THF), and *N*-phenyl-*p*-anisidine (32.5 mg, 55%) was obtained. ^{1}H NMR ($CDCl_3$) δ 3.84 (s, 3H), 6.83–7.26 (m, 9H), The N-H proton could not be detected; ^{13}C NMR ($CDCl_3$) δ 55.54, 114.64, 115.64, 119.54, 122.18, 129.27, 135.70, 145.12, 155.26; IR ($CHCl_3$) 3400, 2820, 1610, 1520, 1510, 1475, 1320, 1310, 1260, 1190, 1050, 850 cm^{-1}. HRMS *m*/*z*: calcd for $C_{13}H_{13}NO$ (M^+) 199.0997, found 199.0973.

***N*-(*tert*-Butyl)-*p*-anisidine (5n):**[20] To a solution of potassium hydroxide (337 mg, 6 mmol) in ethanol (3.0 mL) was added a ethanol (0.5 mL) solution of diethyl 2-[*tert*-butyl(*p*-methoxyphenyl)amino]malonate (42.3 mg, 0.125 mmol) and subsequently iodosylbenzene (41.4 mg, 0.188 mmol) at 0 °C. After stirring for 19 h at room temperature and an additional 22 h at 50 °C, solvent was removed in vacuo, and then sat. NH_4Claq was added. This mixture was extracted with ethyl acetate (5 mL × 3). All organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification was performed by preparative TLC on silica gel (ethyl acetate/hexane =1:10, 3 times) to give *N*-(*tert*-butyl)-*p*-anisidine (15.1 mg, 67%). ^{1}H NMR ($CDCl_3$) δ 1.21 (s, 9H), 2.09 (br, 1H), 3.76 (s, 3H), 6.75–6.83 (m, 4H), The N-H proton could not be detected; ^{13}C NMR ($CDCl_3$) δ 30.07, 52.36, 55.50, 114.03, 122.92, 154.39; IR (neat) 2950, 1655, 1530, 1375, 1240, 1050, 840 cm^{-1}.

Benzyl *N*-Ethyl-*N*-(*p*-methoxyphenyl)carbamate (6a): To a mixture of *N*-ethyl-*p*-anisidine (**5a**) (590 mg, 3.9 mmol), THF (2.0 mL) and aqueous Na_2CO_3 solution (10 mL, 4.0 M), benzyl chloroformate (0.628 mL, 4.4 mmol) and aqueous Na_2CO_3 solution (5 mL, 4.0 M), were successively added at 0 °C. After stirring for 3 h at room temperature, water was added, and the whole mixture was extracted with ethyl acetate (10 mL × 3). The combined extracts were dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography (ethyl acetate/hexane=1:10) to give the title product (1.06 g, 93%). ^{1}H NMR ($CDCl_3$) δ 1.13 (t, J = 7.3 Hz, 3H), 3.68 (q, J = 7.3 Hz, 2H), 3.79 (s, 3H), 5.13 (br, 2H), 6.87 (d, J = 8.9 Hz, 2H), 7.08–7.36 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 13.56, 45.47, 55.34, 66.84, 114.12, 127.65, 128.29, 128.55, 136.87, 155.41, 158.08; IR (neat) 2950, 2920, 1720, 1700, 1620, 1520, 1255, 1165, 1040, 850 cm^{-1}. HRMS *m*/*z*: calcd for $C_{17}H_{19}NO_3$ (M^+) 285.1365, found: 285.1367.

Benzyl *N*-Ethylcarbamate (7a):[21] To an acetonitrile (1.2 mL) solution of benzyl *N*-ethyl-*N*-(*p*-methoxyphenyl)carbamate (42.8 mg, 0.150 mmol), a solution of ammonium cerium(IV) nitrate (247 mg, 0.450 mmol) in water (1.6 mL) was slowly added at −15 °C. This mixture was allowed to warm to −10 °C with stirring for 30 min. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (5 mL × 3). The organic extracts were washed with 5% $NaHCO_3$aq (10 mL), and the aqueous layer was extracted with ethyl acetate (5 mL × 2). The combined organic extracts were washed with 10% $NaHSO_3$aq, 5% $NaHCO_3$aq, and brine, and then dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by preparative TLC on silica gel (ethyl acetate/hexane =1:10) to give benzyl *N*-ethylcarbamate (24.8 mg, 92%). ^{1}H NMR ($CDCl_3$) δ 1.13 (t, J = 7.3 Hz, 3H), 3.23 (quint, J = 7.3 Hz, 2H), 4.75 (br, 1H), 5.09 (s, 2H), 7.26–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.19, 35.88, 66.49, 128.02, 128.06, 128.46, 136.65, 156.25; IR (neat) 3310, 2950, 1710, 1545, 1460, 1270, 1030 cm^{-1}.

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