Pergamon

Tetrahedron Letters 42 (2001) 5473–5476

TETRAHEDRON LETTERS

Electrophilic amination with iminomalonate

Yasuki Niwa, Kazuki Takayama and Makoto Shimizu*

Department of Chemistry for Materials, Mie University, Tsu, Mie 514-8507, Japan

Received 11 May 2001; revised 4 June 2001; accepted 8 June 2001

Abstract—Diethyl *N*-anisyliminomalonate has been found to be an excellent electrophilic amination reagent for Grignard reagents to give *N*-alkylated products in good yields, and subsequent air oxidation affords *N*-alkylanisidines.

Although one of the most important reactions for the preparation of amines involves electrophilic amination of anions, such reactions have not been readily carried out due to the tedious preparation and instability of reagents, lack of the generality, and so on.[1] Recent studies in this field have found several efficient electrophilic aminations with imine derivatives such as oxaziridines,[2] oximes,[3] and oxime *O*-sulfonates.[4] However, there still remains important problems of accessibility of the reagent as well as of the reaction procedure. Hitherto, several reagents have been developed for *N*-alkylation reactions of α-imino esters.[5] In particular, Grignard reagents were proved to be the reagents of choice for this type of *N*-alkylation reaction of α-imino esters.[5a] In our laboratory, we recently described the coupling reaction of α-iminoacetates with dialkylaluminum chloride to give *N*-monoalkylated 1,2-diamines, where efficient *N*-alkylation with alkylaluminum reagents was highly responsible for the success of the new coupling reaction.[6] During these studies we found that imines with two electron-withdrawing substituents possessed good abilities to react with nucleophiles on the nitrogen atoms in a regioselective manner. We wish to report that *N*-anisyliminomalonate **1** is a new efficient electrophilic amination reagent for Grignard reagents to give, after subsequent oxidation with air, *N*-alkylanisidines **5** in good to excellent yields (Fig. 1).

The amination reagent, diethyl *N*-anisyliminomalonate **1** was prepared by condensation of commercially available diethyl ketomalonate **2**[7] with *p*-anisidine in 85% yield (Scheme 1).

First, addition of several ethylation reagents is examined and the results are summarized in Table 1. Ethylaluminum dichloride and diethylaluminum chloride gave the desired *N*-ethylation product **3a** in 32 and 66% yield, respectively with good regioselectivity, whereas diethylzinc in toluene solution afforded **3a** in 80% yield along with the *C*-ethylation product **4a** (entries 1, 2 and 5). The use of ethylmagnesium bromide recorded the formation of the *N*-ethylation product **3a** in 84% yield (entry 6). From the standpoint of accessibility of the alkylation reagents, Grignard reagents were chosen as nucleophiles in the present study. After screening of the solvent and the amount of Grignard reagent, the use of 1.5 equiv. of ethylmagnesium bromide in THF was found to be the most effective to give the *N*-ethylation product **3a** in 91% yield (entry 9).

We next examined oxidative removal of the malonate moiety to obtain *N*-ethylanisidine **5a**, and results are summarized in Table 2.

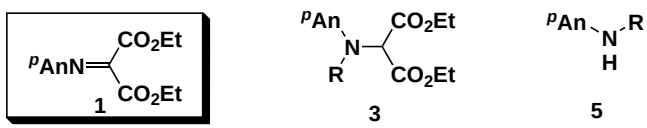
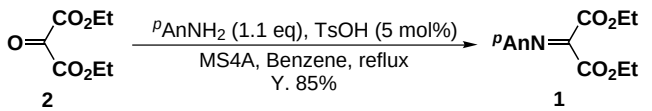


Figure 1.

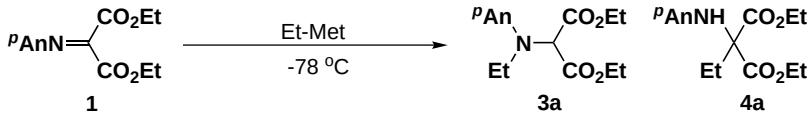


Scheme 1.

* Corresponding author. Tel.: +81-59-231-9413; fax: +81-59-231-9413; e-mail: mshimizu@chem.mie-u.ac.jp

0040-4039/01/$ - see front matter
PII: S0040-4039(01)01022-X

Table 1. Ethylation of iminomalonate **1** using several organometals

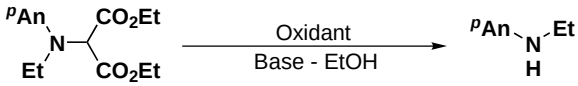


1 3a 4a

Entry	Et-Met (equiv.)	Solvent	Time (min)	Yield of **3a** (%)[a]	Yield of **4a** (%)[a]
1	$EtAlCl_2$ (3)	CH_2Cl_2	65	32	–
2	Et_2AlCl (3)	CH_2Cl_2	18	66	–
3	Et_3Al (3)	CH_2Cl_2	42	25	24
4	Et_2Zn (3)	THF	56	40	23
5	Et_2Zn (3)	Toluene	17	80	15
6	EtMgBr (1.2)	THF	60	84	–
7	EtMgBr (1.2)	Et_2O	10	59	–
8	EtMgBr (1.2)	Toluene	17	50	–
9	EtMgBr (1.5)	THF	48	91	–

[a] Yields were determined by ^1H NMR using pyrazine as internal standard.

Table 2. Oxidative cleavage of *N*-ethylation product **3a**



3a 5a

Entry	Oxidant (equiv.)	Base	Temp. (°C)	Time (h)	Yield (%)[a]
1	$PhI(OAc)_2$ (1.5)	KOH (2 M)	0 ~ rt	17	22
2	$PhI(OTfa)_2$ (1.5)	KOH (2 M)	0 ~ rt	26	54
3	PhIO (1.5)	KOH (2 M)	0 ~ rt	22	82
4	Air	1 M KOH aq (0.44 equiv.)	rt	48	57
5	Air[b]	1 M KOH aq (0.44 equiv.)	rt	47	84
6	O_2	1 M KOH aq (0.44 equiv.)	rt	22.5	45

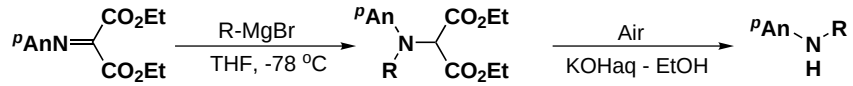
[a] Isolated yields.
[b] Worked up with 10% aqueous Na_2SO_3.

Although iodosobenzene diacetate, known as a mild oxidation reagent for α-hydroxylation of carbonyl compounds, was firstly examined,[8] *N*-ethylanisidine **5a** was obtained in only 22% yield (entry 1). Iodosobenzene was found to be an effective oxidation reagent for this reaction to give the desired product **5a** in 82% yield (entry 3).[9] Since oxidation with air is more inexpensive and convenient,[10] air oxidation was next used for the present transformation to give *N*-ethylanisidine **5a** in 57% yield (entry 4). The yield was improved up to 84% by working up the crude reaction mixture with 10% aqueous Na_2SO_3 (entry 5). In contrast, the use of oxygen itself was not effective to this oxidative cleavage (entry 6).

The use of a variety of Grignard reagents followed by oxidative cleavages was examined, and the results are summarized in Table 3. Alkylation with primary alkyl Grignard reagents proceeded to give *N*-alkylation products, and the subsequent oxidative cleavage also proceeded smoothly to give *N*-alkylanisidines in good to excellent yields (entries 1–7), whereas the use of isopropylmagnesium bromide gave the *N*-alkylation product in 34% yield along with the *C*-alkylated by-product, resulting in the decrease in the yield of the desired product (entry 8). When isopropylation reaction was carried out at –95°C, the yield was improved up to 46%. However, the use of tertiary alkylmagnesium bromide did not give the *N*-alkylation product in satisfactory yield, and the oxidative cleavage did not proceed at all (entry 10). The use of phenylmagnesium bromide met with a moderate success (entry 13).

In conclusion, diethyl *N*-anisyliminomalonate was found to be a good electrophilic amination reagent for alkylmagnesium halides. In particular, this reagent was effective for the amination of primary alkyl Grignard reagents, whereas those of secondary, tertiary alkyl, and aryl Grignard reagents gave the desired products in slightly lower yields. The subsequent oxidative removal of malonate moiety was readily carried out with air, giving *N*-alkylanisidines and oxomalonate which might be used repeatedly. From the standpoint of electrophilic amination, this is the first example where α-imino ester is used as the practical amination reagent possessing a removable *N*-*p*-anisyl group. Furthermore, this regent enables the ready separation of the products, anisidine derivatives, from the reaction mixture due to the lipophilic anisyl moiety.

Table 3. Synthesis of *N*-alkylanisidine with electrophilic amination[a]



1 **3** **5**

Entry	R	Products	Yield of **3** (%)[b,c]	Yield of **5** (%)[d]
1	Methyl	**3b**, **5b**	81	50
2	Ethyl	**3a**, **5a**	91	84
3	*n*-Propyl	**3c**, **5c**	81	79
4	*n*-Butyl	**3d**, **5d**	87	60
5	*n*-Decyl	**3e**, **5e**	78	79
6	*n*-Dodecyl	**3f**, **5f**	94	84
7	*n*-Tetradecyl	**3g**, **5g**	79	71
8	Isopropyl	**3h**, **5h**	34 (46)	68
9	Cyclohexyl	**3i**, **5i**	36 (38)	78
10	*tert*-Butyl	**3j**, **5j**	25	–[e]
11	Phenethyl	**3k**, **5k**	86	89
12	Benzyl	**3l**, **5l**	57 (63)	80
13	Phenyl	**3m**, **5m**	44	99

[a] The reaction was carried out according to the typical procedure (Ref. 11).
[b] Yields were determined by ^{1}H NMR using pyrazine as internal standard.
[c] Yields in the parentheses were obtained from the runs carried out at –95°C.
[d] Isolated yields.
[e] Oxidative cleavage did not proceed.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, of the Japanese Government and a grant from Nagase Science and Technology Foundation.

References

1. (a) Greck, C.; Genêt, P. *Synlett* **1997**, 741; (b) Erdik, E.; Ay, M. *Chem. Rev.* **1989**, *89*, 1947.
2. (a) Page, P. C. B.; Murrell, V. L.; Limousin, C.; Laffan, D. D. P.; Bethell, D.; Slawin, A. M. Z.; Smith, T. A. D. *J. Org. Chem.* **2000**, *65*, 4204; (b) Armstrong, A.; Atkin, M. A.; Swallow, S. *Tetrahedron Lett.* **2000**, *41*, 2247; (c) Enders, D.; Poiesz, C.; Joseph, R. *Tetrahedron: Asymmetry* **1998**, *9*, 3709; (d) Vidal, J.; Damestoy, S.; Guy, L.; Hannachi, J.-C.; Aubry, A.; Collet, A. *Chem. Eur. J.* **1997**, *3*, 1691; (e) Vidal, J.; Guy, L.; Stérin, S.; Collet, A. *J. Org. Chem.* **1993**, *58*, 4791; (f) Andreae, S.; Schmitz, E.; Wulf, J.-P.; Schulz, B. *Liebigs. Ann. Chem.* **1992**, 239; (g) Andreae, S.; Schmitz, E. *Synthesis* **1991**, 327.
3. Alvernhe, G.; Laurent, A. *Tetrahedron Lett.* **1972**, 1007.
4. (a) Tsutsui, H.; Ichikawa, T.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1869; (b) Erdik, E.; Daskapan, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3139; (c) Erdik, E.; Daskapan, T. *Synth. Commun.* **1999**, *29*, 3989; (d) Tsutsui, H.; Hayashi, Y.; Narasaka, K. *Chem. Lett.* **1997**, 317; (e) Erdik, E.; Ay, M. *Synth. React. Inorg. Met.-Org. Chem.* **1989**, *19*, 663; (f) Hagopian, R. A.; Therien, M. J.; Murdoch, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 5753.
5. (a) Fiaud, J.-C.; Kagan, H. B. *Tetrahedron Lett.* **1971**, 1019; (b) Yamamoto, Y.; Ito, W. *Tetrahedron* **1988**, *44*, 5415; (c) Uneyama, K.; Yan, F.; Hirama, S.; Katagiri, T. *Tetrahedron Lett.* **1996**, *37*, 2045; (d) Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. *Synlett* **1999**, 1148.
6. Shimizu, M.; Niwa, Y. *Tetrahedron Lett.* **2001**, *42*, 2829.
7. Diethyl ketomalonate **2** is also synthesized readily. See: (a) Tietze, L. F.; Bratz, M. *Org. Synth.* **1992**, *71*, 214; (b) Wasserman, H. H.; Han, W. T. *Tetrahedron Lett.* **1984**, *25*, 3743; (c) Jung, M. E.; Shishido, K.; Davis, L. H. *J. Org. Chem.* **1982**, *47*, 891; (d) Pardo, S. N.; Salomon, R. G. *J. Org. Chem.* **1981**, *46*, 2598; (e) Dox, A. W.; *Org. Synth., Coll.* Vol. 1 **1941**, 266; (f) Gilman, E.; Johnson, T. B. *J. Am. Chem. Soc.* **1928**, *50*, 3341.
8. (a) Moriarty, R. M.; Prakash, O.; Karalis, P.; Prakash, I. *Tetrahedron Lett.* **1984**, *25*, 4745; (b) Moriarty, R. M.; Hu, H. *Tetrahedron Lett.* **1981**, *22*, 2747.
9. Moriarty, R. M.; Hu, H.; Gupta, S. C. *Tetrahedron Lett.* **1981**, *22*, 1283.
10. Crombie, L.; Godin, P. J. *J. Chem. Soc.* **1961**, 2861.
11. <Ethylation reaction>Under an argon atmosphere, to a solution of diethyl *N*-anisyliminomalonate (83.8 mg, 0.300 mmol) in THF (3.75 mL), EtMgBr (0.450 mmol, 0.971 M in THF) was slowly added at –78°C. After 48 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. Yield was determined by ^{1}H NMR using pyrazine as an internal standard to indicate the

formation of diethyl 2-(*N*-ethyl-*N*-anisylamino)malonate in 91%.

<Oxidative cleavage>The crude diethyl 2-(*N*-ethyl-*N*-anisylamino)malonate (0.240 mmol) was dissolved in a mixture of 1.0 M KOH (0.106 mL) and EtOH (3.06 mL), and the whole solution was vigorously stirred. After 47 h, 10% aqueous Na_2SO_3 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 on preparative silica gel TLC (AcOEt/hexane = 1:10) to give *N*-ethylanisidine (30.3 mg, 84%).