Pergamon

Tetrahedron Letters 42 (2001) 2829–2832

TETRAHEDRON LETTERS

N-Alkylation-coupling reaction of imines promoted by alkylaluminum reagents, leading to a facile synthesis of 1,2-diamines

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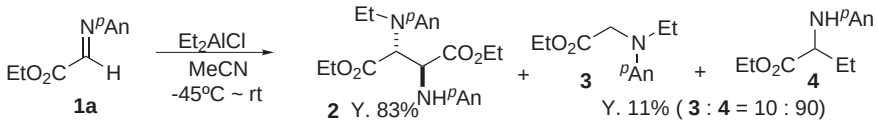
Received 14 February 2001; revised 17 February 2001; accepted 21 February 2001

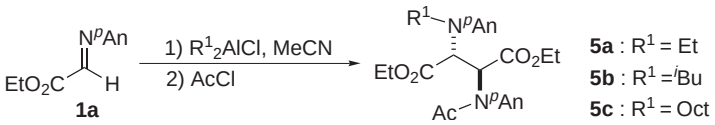
Abstract—*N*-Alkylation-coupling reactions of the imines derived from glyoxylate esters were conducted with dialkylaluminum chloride in acetonitrile to give *N*-monoalkylated 1,2-diamines in good yields. © 2001 Published by Elsevier Science Ltd.

1,2-Diamines are useful units for the synthesis of biologically active compounds[1] and/or widely used as ligands in many transition metal mediated reactions[2] and, therefore, new synthetic methods of 1,2-diamines have been studied extensively over the past few years.[3] 1,2-Diamine syntheses, along with carbon–carbon bond formation, have been reported using iminopinacol coupling reactions,[4] nitro-Mannich reactions,[5] 1,3-dipolar cycloadditions,[6] and addition of α-nitrogen anions to imines.[7] In our laboratory, 1,2-diamines were stereoselectively obtained by iminopinacol coupling reactions using a Zn–Cu couple and (+)-camphorsulfonic acid.[8] We report here a new method of 1,2-diamine synthesis using a coupling reaction of the imines derived from ethyl glyoxylate promoted by alkylaluminum reagents.



Scheme 1.

Table 1. Coupling reactions using $R^1{}_2AlCl$[a]



$R^1{}_2AlCl$ (equiv.)	Yield (%)[b]	*anti*:*syn*[c]
Et_2AlCl (5 equiv.)	79	70:30
iBu_2AlCl (5 equiv.)	59	90:10
iBu_2AlCl (7 equiv.)	61	88:12
Oct_2AlCl (5 equiv.)	81	62:38
Oct_2AlCl (7 equiv.)	95	72:28

[a] Reaction was carried out according to the typical procedure.
[b] Isolated yield.
[c] Based on isolated products.

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0040-4039/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0040-4039(01)00302-1

First, the reaction of *p*-anisylimine **1a**, prepared by condensation of ethyl glyoxylate with *p*-anisidine, was examined using diethylaluminum chloride in acetonitrile. We found that the *N*-monoethylated coupling product **2** was obtained along with *N*- and *C*-ethylated products **3** and **4** (Scheme 1). This type of *N*-alkylation reaction has been reported by van Koten,[9] who obtained β-lactams in 80–90% yields instead of diamines, and some *N*-ethylation reactions have been also reported.[10]

The use of other organoaluminum reagents, such as diisobutylaluminum chloride and dioctylaluminum chloride, was also examined and a typical experimental procedure is as follows: an acetonitrile solution (0.7 mL) of aluminum reagent (0.724 mmol) was added to ethyl *N*-anisyliminoacetate (0.145 mmol) in acetonitrile (0.25 mL) at −45°C. After stirring for 1 hour, acetyl chloride (0.724 mmol) was added to this solution. Usual work-up, followed by purification on silica gel TLC, gave the coupling product (28.1 mg, 79%) as a colourless oil. Results using a variety of organoaluminum reagents are summarised in Table 1.

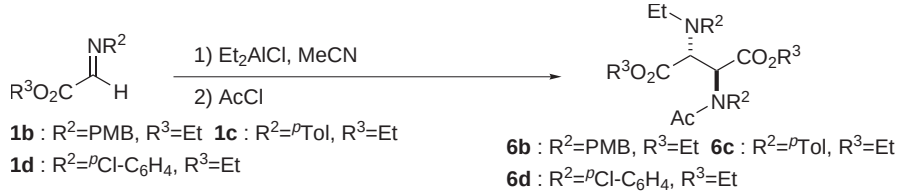
Diethylaluminum chloride effected the *N*-alkylation-coupling reaction and product **5a** was obtained in 79% yield with a ratio of *anti*:*syn*=70:30, whereas the use of diisobutylaluminum chloride gave the coupling product **5b** in 61% yield, along with the reduction product in 10% yield. In the case of dioctylaluminum chloride, the desired product **5c** was obtained in high yield. In each case, *anti*-selectivity was observed in which a bulky R^1 group resulted in a good diastereoselectivity. Diisobutylaluminum chloride and dioctylaluminum chloride, used in the present study, were prepared by the disproportionation of the corresponding trialkylaluminums and aluminum chloride in *n*-hexane. When triethylaluminum or ethylaluminum dichloride was used, the coupling product **2** was not formed but the *C*-ethylation product **3** (24%) or a mixture of *C*- and *N*-ethylation products (**3**:**4**=29:71, 66%) was obtained, respectively. The amount of diethylaluminum chloride is also important. For example, the use of 3 equiv. of diethylaluminum chloride decreased the formation of the desired coupling product **2** to 33% yield along with the ethylation products (**3**:**4**=47:53, 58% yield). This may be due to the competing *C*-alkylation reaction caused by the low aggregated alkylaluminum species, whereas the use of a large excess of the aluminum reagent suppresses *C*-alkylation.

Next, effects of the substituent of the imino group were investigated using diethylaluminum chloride. Imines **1b–d** were readily prepared from ethyl glyoxylate and the corresponding amines were obtained by condensation. The results are summarised in Table 2.

The coupling reaction of *p*-methoxybenzylimine **1b** gave no desired product, presumably due to the steric hindrance caused by the unfixed sp^3 carbon and/or the low conjugated aliphatic *N*-substituent, whereas the use of aromatic imines, such as *p*-tolylimine **1c** and *p*-chlorophenylimine **1d**, gave the desired products in 62 and 41% yields, respectively. In order to improve the diastereoselectivity, the ester part of the α-iminoester was screened and the results are summarised in Table 3. The reaction was carried out under the same conditions as in the above cases except for trapping with trifluoroacetic anhydride in place of acetyl chloride. The coupling reaction of ethyl ester **1a** gave 1,2-diamine **7a** in 80% yield with a 66:34 ratio of the diastereomers. Using oxygen-free acetonitrile, the diastereoselectivity was improved up to 81:19. The isopropyl ester **1e**, which has a more sterically hindered group, gave the 1,2-diamine **7b** in 80% yield with a 76:24 diastereoselectivity. The cyclohexyl ester **1f** gave a slightly lower yield but had a better selectivity of *anti*:*syn*=86:14.

The relative stereochemistry was determined as follows. *N*-Ethylated coupling product **2** was exposed to isopropylmagnesium bromide in diethyl ether solution and cyclised to β-lactam in 32% yield (Scheme 2). The coupling constant between H_3 and H_4 was 1.98 Hz in the major isomer, while J=4.95 Hz in the minor isomer. Therefore, the major isomer of this azetidinone was determined to be *trans* and, hence, the corresponding diamine **2** has an *anti* configuration.

Table 2. Effects of the substituent of the imino group[a]



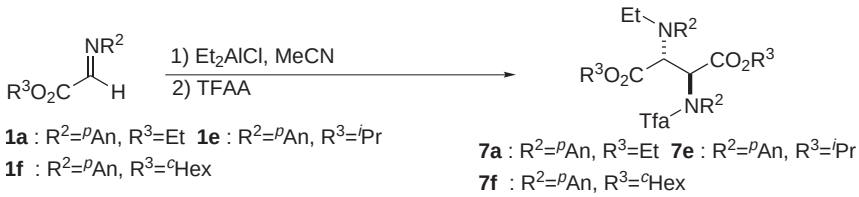
1b : R^2=PMB, R^3=Et **1c** : R^2=^{p}Tol, R^3=Et
1d : R^2=^{p}Cl-C_6H_4, R^3=Et

6b : R^2=PMB, R^3=Et **6c** : R^2=^{p}Tol, R^3=Et
6d : R^2=^{p}Cl-C_6H_4, R^3=Et

Imine	Yield (%)[b]	*anti*:*syn*[c]
1b	0	–
1c	62	75:25
1d	41	66:34

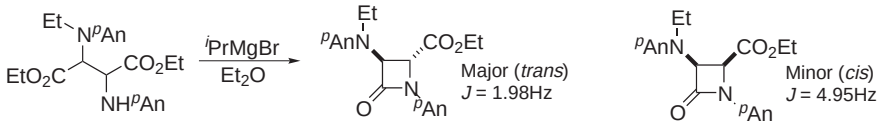
[a] Reaction was carried out according to the typical procedure.
[b] Isolated yield.
[c] Based on isolated products.

Table 3. Effects of the ester group

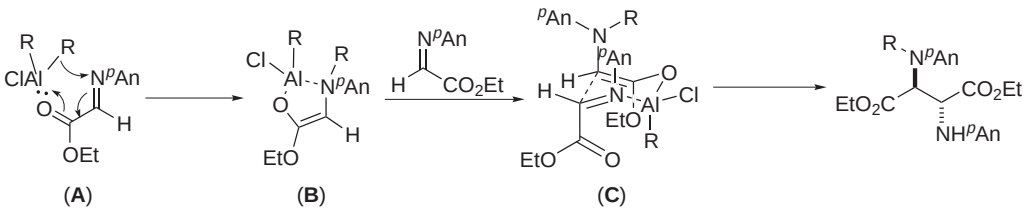


Imine	Yield (%)[a]	*anti*:*syn*[b]
1a	80	66:34
1a[c]	79	81:19
1e	80	76:24
1f	62	86:14

[a] Isolated yield.
[b] Determined by HPLC.
[c] Oxygen-free acetonitrile was used.



Scheme 2.



Scheme 3.

A possible mechanism for this coupling reaction is shown in Scheme 3. Dialkylaluminum chloride, which has a strong oxophilicity, initially coordinates with the ester carbonyl group (**A**), making the electron density of the nitrogen atom decrease. Then, 1,4-addition of alkyl group of the aluminum reagent proceeds on the nitrogen atom to form the ester enolate (**B**), which has a five-membered (*Z*)-conformation because of coordination of the aluminum with the nitrogen atom. This ester enolate attacks another imine via a chair-like, six-membered cyclic transition state (**C**) to give the *anti*-coupling product. An alternative mechanism involving a single electron transfer is also possible. We are currently investigating this possibility in more detail.

In conclusion, dialkylaluminum chlorides promoted an *N*-alkylation-coupling reaction of α-iminoacetates in acetonitrile to give diamines in good yields. The diastereoselectivity was improved using sterically hindered esters. Since the reaction appears to be applicable to a series of dialkylaluminum chlorides, this reaction may be used for the synthesis of 1,2-diamines of biological interest. Applications of the present reaction to the cross-coupling with other imines or aldehydes are currently under active investigation.

References

1. (a) De Clercp, P. J. *Chem. Rev.* **1997**, *97*, 1755; (b) Kulanthaivel, P.; Hallock, Y. F.; Boros, C.; Hamilton, S. M.; Janzen, W. P.; Ballas, L. M.; Loomis, C. R.; Jiang, B.; Katz, B.; Steiner, J. R.; Clardy, J. *J. Am. Chem. Soc.* **1993**, *115*, 6452; (c) Otsuka, M.; Matsda, T.; Haupt, A.; Ohno, M.; Shiraki, T.; Sugiura, Y.; Maeda, K. *J. Am. Chem. Soc.* **1990**, *112*, 838; (d) Stubbe, J.; Kozarich, J. K. *Chem. Rev.* **1987**, *87*, 1107; (e) Gardiner, R. A.; Rinehart, Jr., K. L.; Snyder, J. J.; Broquist, H. P. *J. Am. Chem. Soc.* **1968**, *90*, 5639; (f) Baldwin, J. E.; Adlington, R. M.; Birch, D. J. *J. Chem. Soc.* **1962**, 583.
2. (a) Bennari, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161; (b) Togni, A.; Venanzi, L. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 497; (c) Tomioka, K. *Synthesis* **1990**, 541; (d) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581.
3. (a) Lucent, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2580; (b) Enders, D.; Schiffers, R. *Synthesis* **1996**, 1013; (c) Shimizu, M.; Kamei, M.; Fujisawa, T. *Tetrahedron Lett.* **1995**, *36*, 8607; (d) Dondoni, A.; Merchan, F. L.; Merino, P.; Tejero, T.; Bertolasi, V. *J. Chem. Soc., Chem. Commun.* **1994**, 1731; (e) Reetz, M. T.; Hübel, M.; Jaeger, R.; Schwickardi, R.; Goddard, R. *Synthesis* **1994**, 733; (f)

Reetz, M. T.; Jaeger, R.; Drewlies, R.; Hübel, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 103.

4. (a) Periasamy, M.; Karunakar, G. V.; Bharathi, P. *Tetrahedron Lett.* **1999**, *40*, 7577; (b) Dutta, M. P.; Baruah, B.; Baruah, A.; Prajapati, D.; Sandhu, J. S. *Synlett* **1998**, 857; (c) Alexakis, A.; Aujard, I.; Mangeney, P. *Synlett* **1998**, 873; (d) Hatana, B.; Ogawa, A.; Hirao, T. *J. Org. Chem.* **1998**, *63*, 9421; (e) Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron Lett.* **1998**, *39*, 3333; (f) Baruah, B.; Prajapati, D.; Sandhu, J. S. *Tetrahedron Lett.* **1995**, *36*, 6747; (g) Imamoto, T.; Nishimura, S. *Chem. Lett.* **1990**, 1141; (h) Tanaka, H.; Dhimane, H.; Fujita, H.; Ikemoto, Y.; Torii, S. *Tetrahedron Lett.* **1988**, *29*, 3811; (i) Roskamp, E. J.; Pederson, S. F. *J. Am. Chem. Soc.* **1987**, *109*, 3152.
5. (a) Anderson, J. C.; Peace, S.; Pih, S. *Synlett* **2000**, 850; (b) Adams, H.; Anderson, J. C.; Peace, S.; Pennell, A. M. K. *J. Org. Chem.* **1998**, *63*, 9932.
6. (a) Alker, D.; Harwood, L. M.; Williams, C. E. *Tetrahedron Lett.* **1998**, *39*, 475; (b) Viso, A.; Fernández de la Pradilla, R.; Strachan, C.-G.; Alonso, M.; Ripoll, M.-M.; André, I. *J. Org. Chem.* **1997**, *62*, 2316; (c) Amornraksa, K.; Barr, D.; Donegan, G.; Grigg, R.; Ratananukul, P.; Sridharan, V. *Tetrahedron* **1989**, *45*, 4649.
7. (a) Park, Y. S.; Boys, M. L.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 3757; (b) Kise, N.; Kashiwagi, M.; Yoshida, J. *J. Org. Chem.* **1996**, *61*, 428; (c) Ahlbrecht, H.; Schmitt, C. *Synthesis* **1994**, 719; (d) Savignac, P.; Leroux, Y.; Normant, H. *Tetrahedron* **1975**, *31*, 877.
8. Shimizu, M.; Iida, T.; Fujisawa, T. *Chem. Lett.* **1995**, 609.
9. van Vliet, M. R. P.; Jastrzebski, J. T. B. H.; Klaver, W. J.; Goubitz, K.; van Koten, G. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 132.
10. (a) Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. *Synlett* **1999**, 1148; (b) Uneyama, K.; Yan, F.; Hirama, S.; Katagiri, T. *Tetrahedron Lett.* **1996**, *37*, 2045; (c) Yamamoto, Y.; Ito, W. *Tetrahedron* **1988**, *44*, 5415; (d) Fiaud, J.-C.; Kagan, H. B. *Tetrahedron Lett.* **1971**, 1019.