Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 6487–6491

TETRAHEDRON LETTERS

Structural sensitivity in phosphorylation of enamines—derivatives of β-aminocrotonic acid with diphenylchlorophosphine

Alexandr N. Kostyuk,* Yurii V. Svyaschenko, Dmitriy M. Volochnyuk, Nikolai V. Lysenko, Andrei A. Tolmachev and Alexandr M. Pinchuk

Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Murmanskaya 5, Kiev 94, 02094, Ukraine

Received 11 April 2003; revised 7 June 2003; accepted 20 June 2003

Abstract—The reaction of 'push–pull' enamines—derivatives of β-aminocrotonic acid with diphenylchlorophosphine has been investigated. Structural sensitivity of the reaction was found and is discussed.

β-Enaminones and β-enaminonitriles are widely used as building blocks in organic synthesis.[1,2] Thus, development of methods for further functionalization of these compounds is a worthwhile investigation. Continuing our research directed at the study of phosphorylation of enamines with phosphorus(III) halides[3] we report on our results of phosphorylation of 'push–pull' enamines—derivatives of aminocrotonic acid with diphenylchlorophosphine. Although some papers have dealt with this issue, only a limited number of successful phosphorylations of linear enamines have been reported so far. Among these it is worth noting the phosphorylation of bis(diethylamino)ethylene, which gave stable phosphorylated linear enamine derivatives. In most cases it is not possible to prepare stable derivatives of phosphorylated enamines due to the highly labile C–P bond.[4] We expected that the introduction of an electron-accepting group at the β-position of the enamine would increase the stability of the C–P bond, thus giving an opportunity to prepare stable phosphorylated derivatives. Four starting 'push–pull' enamine derivatives of aminocrotonic acid were chosen for our investigations, which are shown in Figure 1.

Our studies revealed that phosphorylation was very sensitive to the structure of the enamine. Thus, enamine **1a** is readily phosphorylated with diphenylchlorophosphine in methylene chloride in the presence of triethylamine. The reaction ran to completion in 24 h giving the expected phosphine **3**. (Scheme 1).[5] The phosphine **3** was transformed into air stable derivatives of phosphorus(V) **4** and **5**,[6,7] as well as into phosphonium salt **6**,[8] which were separated and purified (Tables 1–3).

Enamine **1b** appeared to react less selectively. The reaction ran to completion in 3 days giving a complex mixture as monitored by ^{31}P NMR spectroscopy. Nevertheless, further oxidation of the reaction mixture with sulfur or hydrogen peroxide resulted in stable derivatives **4b**, **5b**[5,6] which were separated in moderate yields.

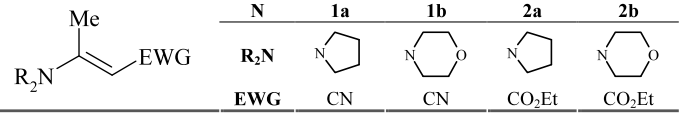
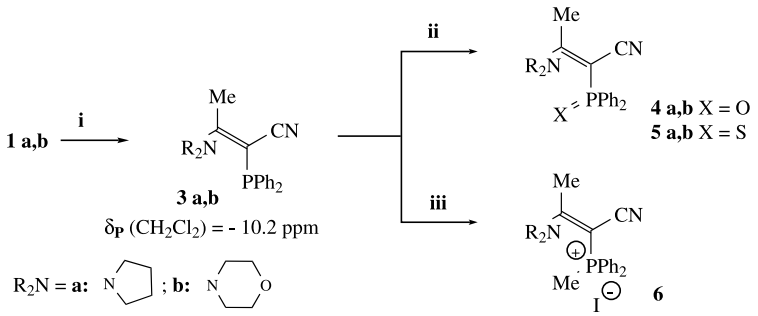


Figure 1. The structure of starting 'push–pull' enamines.

Keywords: enamines; diphenylchlorophosphine; phosphorylation.
* Corresponding author.

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01546-6



Scheme 1. *Reagents and conditions*: (**i**) Ph_2PCl, CH_2Cl_2, Et_3N, for **a**: 24 h, for **b**: 3 days; (**ii**) for **4**: $(NH_2)_2CO{\cdot}H_2O_2$, CH_2Cl_2; for **5**: S, CH_2Cl_2; (**iii**) MeI, CH_2Cl_2.

Table 1. Yields, melting points, solvents for crystallization, ^{31}P NMR data and M^+ of compounds **4–6** and **8–13**[a]

N	Mp (°C)[b]	Yield (%)[c]	^{31}P NMR, δ (ppm)[d]	Solvent	M^+ (m/z)[e]
4a	165–167	46	31.0	Toluene	336
4b	163–165	23	30.4	*i*-PrOH	352
5a	165	37	44.1	*i*-PrOH	352
5b	210–213	25	43.7	*i*-PrOH	368
6[f]	–	64	21.8	–	–
8a	113–115	56	30.7	Heptane	383
8b	113–116	35	31.0	*i*-PrOH	399
9a	134–135	36	42.9	EtOH	399
9b	147–150	30	42.5	EtOH	415
10	91–95	84	27.2	*i*-PrOH:heptane ~ 1:2	330
11	82–83	79	35.9	*i*-PrOH:heptane ~ 1:2	346
12a	136–141	96	–	Benzene	289
12b	143–145	64	–	Benzene	305
13a	129–132	79	–	Cyclohexane	336
13b	114–115	62	–	Cyclohexane	352

[a] Satisfactory microanalysis were obtained: for **4–6**, **8**, and **9** N±0.3%; P±0.4%, for **10** and **11** P±0.3%; for **12** and **13** N±0.3%; S±0.3%.
[b] Melting points are uncorrected.
[c] Yields refer to pure isolated products.
[d] In $CHCl_3$, 121 MHz.
[e] Mass spectra were obtained on a MX-1321 instrument (EI, 70 eV) by direct inlet.
[f] Amorphous solid.

The enamines **2**, derivatives of the ethyl ester of β-aminocrotonic acid, unlike the enamines **1**, were phosphorylated with diphenylchlorophosphine not at the β-position, but at the methyl group giving phosphine **7** (Scheme 2). It should be noted that the reaction is very susceptible to the reaction conditions. Thus, in benzene in the presence of triethylamine no reaction took place. In pyridine the reaction proceeded non-regioselectively and very slowly. The solvent of choice appeared to be methylene chloride in the presence of triethylamine, the reaction going to completion in 24 h giving phosphine **7**.[5] Use of a more active phosphorylating agent, i.e. diphenylbromophosphine, in benzene also afforded **7**.[9] The phosphines **7** were oxidized with sulfur or hydrogen peroxide to the corresponding derivatives **8** and **9**.[6,7] Under mild acidic conditions these pentavalent derivatives were hydrolyzed to the corresponding γ-phosphorylated acetoacetic acids **10** and **11**,[10] which have wide potential synthetic applications.[11]

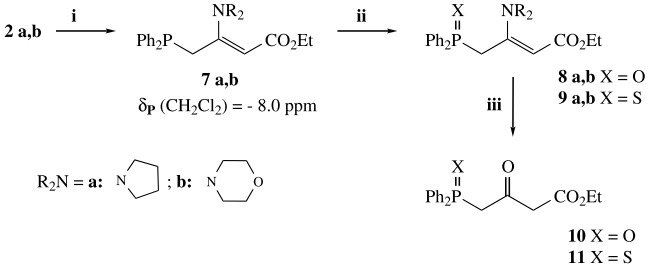
Electrophilic substitution reaction at the γ-position of the 'push–pull' enamines of this type is not typical. Reaction at the γ-position proceeds in the cases of such active electrophiles as isocyanates or in cyclization reactions.[12,13] It should be noted that in all these cases the β-position is also involved. To best of our knowledge, reactions of such enamines which proceed only at the γ-position were previously not known.

To study this reaction in more detail we investigated the reaction of the enamines with the closest hetero analogue of halogen phosphines—arylsulfenyl chloride. In all four cases the reaction proceeded at the β-position giving sulfenylated enamine derivatives (Scheme 3).[14] One can suppose that the difference in the course of the reactions can be attributed to steric factors. To check this proposal, we carried out the sulfenylation of enamine **2b** with sterically hindered trityl sulfenyl chloride under the conditions of phosphorylation (the same

Table 2. ^{1}H NMR data of compounds **4–6** and **8–13**

N	^{1}H NMR (300 MHz), δ (ppm), J (Hz)				
	NR_2	EWG	C(2)H	C(4)H	Ph_2PX or RS
4a[a]	1.96 (4H, bm), 3.51 (2H, bm), 3.92 (2H, bm)	–	–	2.28 (3H, s)	7.42–7.58 (6H, m), 7.80 (4H, dd, $^3J_{HH}=6.9$, $^3J_{PH}=12.3$)
4b[a,d]	3.73–3.77 (8H, m)	–	–	2.35 (3H, s)	7.44–7.58 (6H, m), 7.78 (4H, dd, $^3J_{HH}=6.9$, $^3J_{PH}=12.3$)
5a[a]	1.94 (4H, bm), 3.5 (2H, bm), 3.87 (2H, bm)	–	–	2.23 (3H, s)	7.42–7.58 (6H, m), 7.80 (4H, dd, $^3J_{HH}=7.5$, $^3J_{PH}=12.6$)
5b[a]	3.58–3.85 (8H, m)			2.3 (3H, s)	7.41–7.61 (m, 6H), 7.89 (4H, dd, $^3J_{HH}=6.9$, $^3J_{PH}=12.9$)
6[a]	2.01–2.15 (4H, m), 3.79 (2H, m), 4.05 (2H, m)	–	–	2.14 (3H, s)	2.76 (3H, d, $^2J_{PH}=12.6$), 7.61–7.95 (10H, m)
8a[c]	1.26 (4H, b), 2.54 (2H, b), 3.76 (2H, b)	1.10 (3H, t, $^3J_{HH}=6.9$), 4.09 (2H, q, $^3J_{HH}=6.9$)	4.49 (1H, d, $^4J_{PH}=1.8$)	4.50 (2H, b)	7.04–7.17 (6H, m), 8.31 (4H, dd, $^3J_{HH}=6.9$, $^3J_{PH}=12.3$)
8b[a]	3.27 (4H, t, $^3J_{HH}=4.5$), 3.76 (4H, t, $^3J_{HH}=4.5$)	1.20 (3H, t, $^3J_{HH}=6.9$), 4.02 (2H, q, $^3J_{HH}=6.9$)	4.59 (1H, d, $^4J_{PH}=1.8$)	4.48 (2H, d, $^2J_{PH}=14.1$)	7.42–7.58 (6H, m), 7.80 (4H, dd, $^3J_{HH}=6.9$, $^3J_{PH}=12.3$)
9a[a]	1.92 (4H, bm), 3.05–3.95 (4H, b)	1.05 (3H, t, $^3J_{HH}=6.9$), 3.68 (2H, q, $^3J_{HH}=6.9$)	4.35 (1H, d, $^4J_{PH}=3.6$)	5.01 (2H, b)	7.42–7.58 (6H, m), 7.98 (4H, dd, $^3J_{HH}=7.5$, $^3J_{PH}=12.6$)
9b[a]	3.18 (4H, t, $^3J_{HH}=4.5$), 3.74 (4H, t, $^3J_{HH}=4.5$)	1.42 (3H, t, $^3J_{HH}=6.9$), 3.95 (2H, q, $^3J_{HH}=6.9$)	4.64 (1H, d, $^4J_{PH}=1.8$)	4.65 (2H, d, $^2J_{PH}=13.8$)	7.42–7.58 (6H, m), 7.98 (4H, dd, $^3J_{HH}=7.5$, $^3J_{PH}=12.6$)
10[a]	–	1.23 (3H, t, $^3J_{HH}=6.9$), 4.13 (2H, q, $^3J_{HH}=6.9$)	3.73 (2H, s)	3.80 (2H, d, $^2J_{PH}=15.0$)	7.45–7.56 (6H, m), 7.75 (4H, dd, $^3J_{HH}=6.9$, $^3J_{PH}=12.3$)
11[a,e]	–	1.24 (3H, t, $^3J_{HH}=6.9$), 4.13 (2H, q, $^3J_{HH}=6.9$)	3.76 (2H, s)	3.98 (2H, d, $^2J_{PH}=15.0$)	7.45–7.55 (6H, m), 7.83 (4H, dd, $^3J_{HH}=7.2$, $^3J_{PH}=12.6$)
12a[a,d]	2.03 (4H, bt), 3.81 (4H, b)	–	–	2.23 (3H, s)	7.28 (1H, t, $^3J_{HH}=8.1$), 7.55–7.69 (2H, m), 8.28 (1H, d, $^3J_{HH}=8.1$)
12b[b,d]	3.76 (8H, s)	–	–	2.25 (3H, s)	7.43 (1H, t, $^3J_{HH}=7.2$), 7.54 (1H, d, $^3J_{HH}=7.2$), 7.77 (1H, t, $^3J_{HH}=7.2$), 8.28 (1H, d, $^3J_{HH}=7.2$)
13a[c]	1.19 (4H, b), 2.89 (4H, b)	0.88 (3H, t, $^3J_{HH}=6.9$), 4.06 (2H, q, $^3J_{HH}=6.9$)	–	1.88 (3H, s)	6.55 (1H, t, $^3J_{HH}=8.4$), 6.97 (1H, t, $^3J_{HH}=8.4$), 7.60 (1H, d, $^3J_{HH}=8.4$), 7.99 (1H, d, $^3J_{HH}=8.4$)
13b[c]	2.91 (4H, bm), 3.25 (4H, bm)	0.88 (3H, t, $^3J_{HH}=6.9$), 4.00 (2H, q, $^3J_{HH}=6.9$)	–	1.86 (3H, s)	6.56 (1H, t, $^3J_{HH}=8.4$), 6.94 (1H, t, $^3J_{HH}=8.4$), 7.43 (1H, d, $^3J_{HH}=8.4$), 7.97 (1H, d, $^3J_{HH}=8.4$)
14[a,d,f]	3.21 (4H, t, $^3J_{HH}=4.5$), 3.71 (4H, t, $^3J_{HH}=4.5$)	1.25 (3H, t, $^3J_{HH}=6.9$), 4.09 (2H, q, $^3J_{HH}=6.9$)	–	2.41 (3H, s)	7.05–7.35 (15H, m)

[a] $CDCl_3$.
[b] DMSO-d_6.
[c] C_6D_6.
[d] This substance exists as a mixture of Z/E isomers, ^{1}H NMR spectra refer to the major isomer.
[e] **11** exists as a mixture of keto-enol forms ~10:1, ^{1}H NMR spectra refer to the keto-form.
[f] ^{1}H NMR spectra obtained for crude product.



Scheme 2. *Reagents and conditions*: (**i**), PH_2PCl, CH_2Cl_2, Et_3N, 24 h; (**ii**) for **8**: $(NH_2)_2CO{\cdot}H_2O_2$, CH2Cl2; for **9**: S, CH_2Cl_2; (**iii**) aq. HCl, CH_2Cl_2, rt, 3 days.

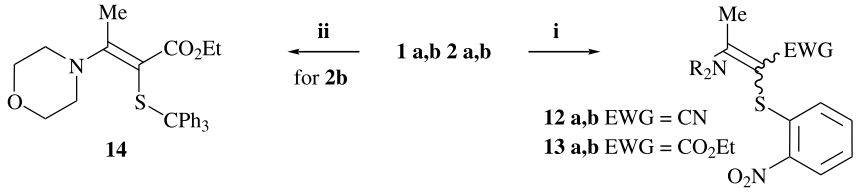
solvent, triethylamine). Although, we failed to separate the final product in analytically pure form due to the high lability of the trityl group at the sulfur atom, NMR analysis of the crude product provided evidence that the reaction proceeded at the β-position (Scheme 3).

The fact that sterically hindered trityl sulfenyl chloride reacted at the β-position refutes our proposal that phosphorylation at the γ-position is encouraged by steric hindrance, caused by an ester group as compared to a nitrile. This course of the reaction can be rationalized by initial attack of diphenylchlorophosphine at the O atom, like trichloroacetylation of enaminones[15] and

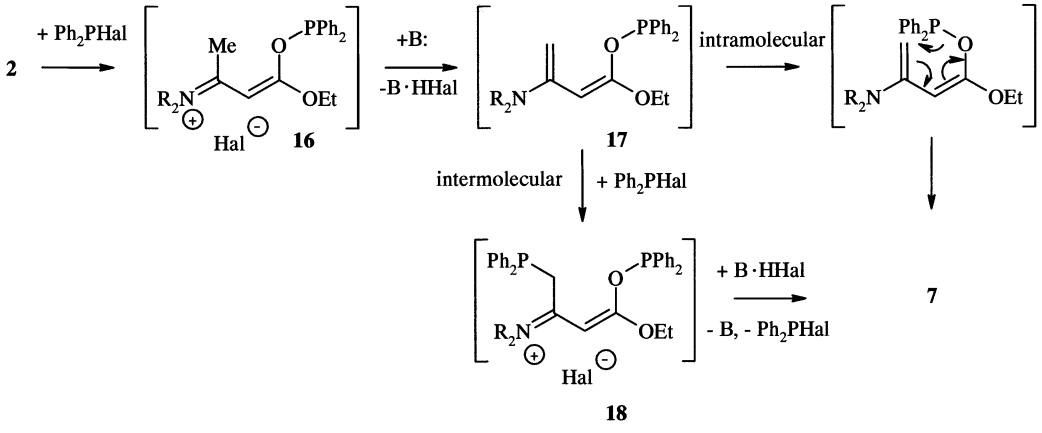
Table 3. ^{13}C NMR data of compounds **4–6** and **8–13**

N	^{13}C NMR (75 MHz), δ (ppm), J (Hz)					
	NR_2	EWG	C(2)	C(3)	C(4)	Ph_2PX or RS
4a[b,c]	24.1 (b), 25.3 (b), 50.8 (b), 51.9 (b)	121.0 ($^2J_{CP}=12.8$)	63.5 ($^1J_{CP}=137.9$)	167.9 ($^2J_{CP}=13.0$)	20.8 ($^1J_{CP}=4.1$)	128.4 ($^2J_{CP}=11.8$), 131.2 ($^3J_{CP}=9.1$), 131.4 ($^4J_{CP}=3.1$), 134.7 ($^1J_{CP}=107.5$)
4b[a]	50.4, 66.7	120.7 ($^2J_{CP}=13.1$)	68.1 ($^1J_{CP}=123$)	171.1 ($^2J_{CP}=11.8$)	20.8 ($^3J_{CP}=3.8$)	128.3 ($^2J_{CP}=12.4$), 131.5 ($^3J_{CP}=9.2$), 131.8 ($^4J_{CP}=3.7$), 133.0 ($^1J_{CP}=109.3$)
8a[a]	25.2, 48.8	14.3, 58.0, 168.6 ($^4J_{CP}=1.5$)	85.1 ($^3J_{CP}=5.2$)	153.9 ($^2J_{CP}=7.5$)	32.9 ($^1J_{CP}=62.0$)	128.0 ($^2J_{CP}=12.1$), 131.4 ($^3J_{CP}=9.0$), 131.6, 131.7 ($^1J_{CP}=103.3$)
8b[a]	47.6, 66.3	14.4, 58.8, 168.8	90.5 ($^3J_{CP}=5.6$)	156.7 ($^2J_{CP}=8.9$)	29.8 ($^1J_{CP}=62.0$)	128.2 ($^2J_{CP}=12.1$), 131.2 ($^3J_{CP}=9.0$), 131.6, 131.7 ($^1J_{CP}=103.3$)
10[a]	–	13.9, 61.2, 166.9	50.7	15.7 ($^2J_{CP}=5.9$)	46.8 ($^1J_{CP}=57.3$)	128.5 ($^2J_{CP}=11.8$), 130.7 ($^3J_{CP}=6.0$), 131.5 ($^1J_{CP}=89.8$), 132.3
13b[a]	51.7, 66.6	14.1, 60.0, 167.8	85.3	166.7	20.4	124.2, 125.9, 126.7, 132.2, 141.3, 144.8

[a] $CDCl_3$.
[b] DMSO-d_6.
[c] Due to hindered rotation about C(3)–N bond signals of pyrrolidine are broad.



Scheme 3. *Reagents and conditions*: **(i)** 2-$NO_2C_6H_4SCl$, Et_3N, PhH, rt, 24 h; **(ii)** Ph_3CSCl, Et_3N, CH_2Cl_2, rt, 3 days.



Scheme 4.

silylation of previously lithiated enamine **2a**,[16] giving rise to intermediate **17**. Then, the phosphorus group migrates either intra- or intermolecularly to give the final product **7** (Scheme 4).

References

1. (a) Kucklaender, U. In *The Chemistry of Enamines*; Rappoport, Z., Ed.; Wiley: Chichester, 1994; Chapter 10, pp.

523–636; (b) Lue, P.; Greenhill, J. V. *Adv. Heterocycl. Chem.* **1997**, *67*, 207–343; (c) Granik, V. G.; Makarov, V. A.; Parkanyi, C. *Adv. Heterocycl. Chem.* **1999**, *72*, 283–359.
2. Erian, A. W. *Chem. Rev.* **1993**, *93*, 1991–2005.
3. (a) Tolmachev, A. A.; Kostyuk, A. N.; Kozlov, E. S.; Chernega, A. N.; Pinchuk, A. M. *Heteroatom Chem.* **1992**, *3*, 163–176; (b) Kostyuk, A. N.; Lysenko, N. V.; Marchenko, A. P.; Koidan, G. N.; Pinchuk, A. M.; Tolmachev, A. A. *Phosphorus Sulfur Silicon Relat. Elem.* **1998**, *139*, 209–229; (c) Kostyuk, A. N.; Volochnyuk, D. M.; Lupiha, L. N.; Pinchuk, A. M.; Tolmachev, A. A. *Tetrahedron Lett.* **2002**, *43*, 5423–5425.
4. (a) Krasavtsev, I. I.; Basalkevich, E. O.; Lozinskii, M. O. *Z. Org. Khim.* **1984**, *6*, 1167–1169; (b) Lazukina, L. A.; Kuhar, V. P.; Pesotskaya, G. V. *Z. Ob. Khim.* **1974**, *44*, 2355–2356.
5. Typical procedure: To a stirred solution of enamine **1** or **2** (40 mmol) and Et_3N (40 mmol) in dichloromethane (50 mL) under dry argon, Ph_2PCl (40 mmol) was added dropwise. In the case of enamines **1a** and **2** only 24 h reaction times were required and in the case of enamine **1b**, the time of reaction was 3 days.
6. To a stirred solution of phosphine **3** or **7**[5] an equimolar amount of $(NH_2)_2CO{\cdot}H_2O_2$ was added, and after 30 min the reaction mixture was washed with water. The organic phase was separated, dried (Na_2SO_4) and concentrated in vacuo. The crude product was crystallized from an appropriate solvent.
7. The product **5** or **9** was prepared according to the procedure applied to the substance **4** or **8**,[6] but instead of $(NH_2)_2CO{\cdot}H_2O_2$, an equimolar amount of elemental sulfur was added.
8. To a stirred solution of phosphine **3a** MeI (50 mmol) was added. After 1 h the reaction mixture was washed with water. The organic phase was separated, dried (Na_2SO_4) and concentrated in vacuo. The crude product was dissolved in boiling isopropanol. After cooling, the solution was decanted from the oil formed and the oil was dried in vacuo.
9. To a stirred solution of enamine 2 (40 mmol) and Et_3N (40 mmol) in benzene (50 mL) under dry argon, Ph_2PBr (40 mmol) was added dropwise. After 24 h the reaction mixture can be used for further transformation.
10. To a stirred solution of **8** or **9** (5 mmol) in dichloromethane (20 mL) 5% aq. HCl (10 mL) was added. After 48 h the organic phase was separated, dried (Na_2SO_4) and concentrated in vacuo. The crude product was crystallized from an appropriate solvent.
11. Ven den Goorbergh, J. A. M.; Van der Gen, A. *Tetrahedron Lett.* **1980**, *21*, 3621–3624.
12. Tsuge, O.; Inaba, A. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 286–290.
13. (a) Tsuge, O.; Inaba, A. *Heterocycles* **1975**, *3*, 1081–1086; (b) Tsuge, O.; Inaba, A. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2828–2832; (c) Belyaeva, O. Y.; Granik, V. G.; Glushkov, R. G.; Vlasova, T. F.; Anisimova, O. S. *Khim. Geterotsikl. Soedin.* **1978**, 798–801.
14. Typical procedure: To a stirred solution of enamine **1** or **2** (40 mmol) and Et_3N (40 mmol) in benzene (25 mL) under dry argon, *o*-$NO_2C_6H_4SCl$ (40 mmol) was added. After 24 h the precipitated solid was filtered off, and benzene was evaporated in vacuo. The residue was triturated with water and crystallized from an appropriate solvent.
15. Böhme, H.; Tränka, M. *Justus Leibigs Ann. Chem.* **1985**, 149–159.
16. Kang, G. J.; Chan, T. H. *Can. J. Chem.* **1985**, *63*, 3102–3110.