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NEW METHODS AND REAGENTS IN ORGANIC SYNTHESIS. 22.[1] DIPHENYL PHOSPHORAZIDATE AS A REAGENT FOR C-ACYLATION OF METHYL ISOCYANOACETATE WITH CARBOXYLIC ACIDS

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Diphenyl phosphorazidate(DPPA) can be used efficiently for the direct C-acylation of methyl isocyanoacetate with carboxylic acids, giving 4-methoxycarbonyloxazoles.

We have disclosed[1] the utility of diethyl phosphorocyanidate for the direct C-acylation of methyl isocyanoacetate with carboxylic acids, giving 5-substituted 4-methoxycarbonyloxazoles. However, when optically active N-protected α-amino acids have been used for the C-acylation, almost racemized oxazoles have been obtained. Investigations to overcome this disadvantage have revealed that diphenyl phosphorazidate(DPPA, $(C_6H_5O)_2P(O)N_3$),[2] in combination with potassium carbonate, can be used for the oxazole synthesis with little racemization.

A typical experimental procedure is as follows(run 10 in Table): To a stirred suspension of Boc-L-Tyr(Bzl)-OH[3](743 mg, 2 mM) and potassium carbonate sesquihydrate[4](661 mg, 4 mM) in dimethylformamide(4 ml) was added methyl isocyanoacetate(793 mg, 8 mM) in dimethylformamide(3 ml) at room temperature. After the mixture was stirred at room temperature for 5 min and then cooled with ice, DPPA(605 mg, 2.2 mM) in dimethylformamide(3 ml) was added. The mixture was stirred at 0-5° for 2 hr and at room temperature for 14 hr. After dilution with benzene-ethyl acetate(1:1, 150 ml), the mixture was successively washed with 30 ml portions of water, 10% aqueous citric acid, water, and saturated aqueous sodium bicarbonate, and dried. The solvent was concentrated and the residue was purified by column chromatography over silica gel(40 g, Merck Art 7734) with benzene-ethyl acetate(4:1) to give the 5-substituted 4-methoxycarbonyloxazole(633 mg, 70%) as colorless crystals. Recrystallization from ethyl acetate-hexane afforded colorless needles(478 mg, 53%).

The results are summarized in Table. Anhydrous potassium carbonate may be used in place of its sesquihydrate, but the efficiency of the C-acylation is inferior(compare run 8 with run 9). Although the use of sodium hydride as a base may afford a less racemized oxazole(see runs 12 and 13), the experimental procedure is rather tedius.[5] Since the C-acylation with achiral acids proceeds straightforwardly(runs 1-3), a slight exess(1.2 eq) of methyl isocyanoacetate is enough to conduct the reaction and purification over silica gel column is not necessary. In the C-acylation with chiral acids, a larger exess(2-5 eq) of methyl isocyanoacetate is required to accomplish the reaction quickly and avoid the racemization. Optically active oxazoles isolated by column chromatography are racemized to some extent.[6] However, when they are crystalline, optically pure oxazoles can be obtained by recrystallization.

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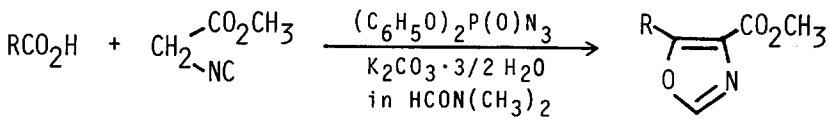
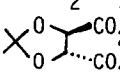
Table. Preparation of 5-Substituted 4-Methoxycarbonyloxazoles[a)]



Run	RCO_2H	Isolated yield,% b)	5-Substituted 4-methoxycarbonyloxazole Mp(rec. solv.) or (Bp/mmHg)	$[\alpha]_D^{23}$ (c=1, MeOH)
1	$C_6H_5CO_2H$ c)	77	91-93°(hexane)	-
2	$C_6H_5CH_2CH_2CO_2H$ c)	(85)	(148°/2)	-
3	Boc-Gly-OH c)	95 (76)	73-75°(Et_2O-hexane)	-
4	Boc-L-Ala-OH	80 (61)	83-85°(Et_2O-pentane)	+19.3°
5	Boc-L-Val-OH	78 (51)	110-112°(Et_2O-hexane)	+11.9°
6	Boc-L-Leu-OH	78 (54)	80-82°(pentane)	-14.2°
7	Boc-L-Met-OH	57 (40)	77-79°(Et_2O-pentane)	-6.98°
8	Boc-L-Phe-OH	70	118-120°(EtOAc-hexane)	+40.8°
9	Boc-L-Phe-OH d)	60		
10	Boc-L-Tyr(Bzl)-OH	70 (53)	129-131°(EtOAc-hexane)	+43.6°
11	Boc-L-Trp-OH	78 (52)	90-93°(Et_2O-pentane)	+58.7°
12	(S) $C_6H_5CH(OCH_2OCH_3)CO_2H$ e)	72	(150°/0.4) f)	-107.4°
13	(S) $C_6H_5CH(OCH_2OCH_3)CO_2H$ g)	70 (66)	(150°/0.4) f)	-116°
14	(R,R)  h) i)	(54)	(130°/0.2) f)	-27.6°

a) Unless otherwise stated, reactions were carried out as described in the text. b) Numbers in parentheses are yields after recrystallization or distillation. c) Methyl isocyanoacetate (1.2 eq) and potassium carbonate sesquihydrate(3.2 eq) were used. d) Anhydrous potassium carbonate was used as a base. e) Methyl isocyanoacetate(5 eq) was used. f) By Kugelrohr distillation. g) Sodium hydride was used as a base. h) J.A. Musich and H. Rapoport, J. Am. Chem. Soc., 100, 4856(1978). i) Potassium carbonate sesquihydrate(3 eq) was used.

References and Notes

1 Part 21, see Y. Hamada, S. Morita, and T. Shioiri, Heterocycles, 17, in press.

2 For a review, see T. Shioiri and S. Yamada, J. Synth. Org. Chem. Japan, 31, 666(1973).

3 Symbols and abbreviations of amino acids are in accordance with recommendations of the IUPAC-IUB Commision on Biochemical Nomenclature, Pure Appl. Chem., 40, 315(1974).

4 Prepared as follows: Anhydrous potassium carbonate was well impregnated with water. After addition of methanol, the potassium carbonate was filtered, washed once with methanol and twice with dioxane, and dried in vacuo. Potassium carbonate sesquihydrate thus obtained was used after pulverization.

5 Prior activation of the starting acid with DPPA as well as prior formation of the carbanion from methyl isocyanoacetate are necessary to conduct the reaction smoothly.

6 For example, the optical purity of the oxazole obtained in run 12 was 72%, which was revealed from its NMR spectrum using a chiral shift reagent, $Eu(facam)_3$.

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