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ONE-POT SYNTHESIS OF α-FLUORO-α,β-UNSATURATED ESTERS FROM CHLOROMALONIC ESTER AND CARBONYL COMPOUNDS USING "SPRAY-DRIED" POTASSIUM FLUORIDE

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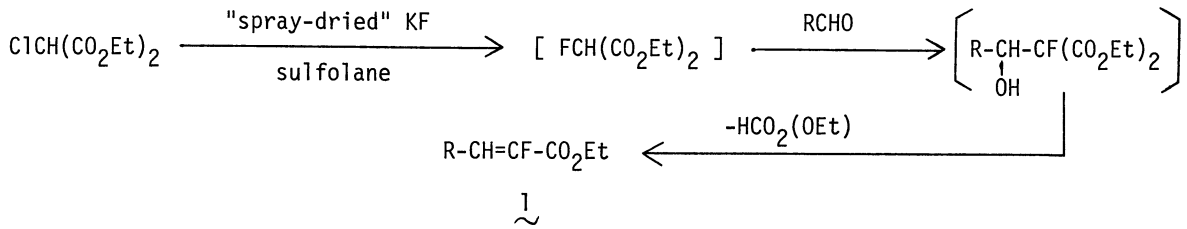
α-Fluoro-α,β-unsaturated esters were prepared by one-pot reaction between aldehydes or ketones and diethyl chloromalonate in the "spray-dried" potassium fluoride-sulfolane system.

In a study of several types of potassium fluoride in organic synthesis, we have revealed that "spray-dried" potassium fluoride[1] possesses a much higher efficiency on the halogen-exchange fluorination compared to "calcine-dried" or "freeze-dried" potassium fluoride.[2,3] This potentiality of the "spray-dried" potassium fluoride is now applied on the preparation of a fluoromalonic ester which is a promisible building block for biologically interesting[4] monofluoro organic molecules. Thus diethyl chloromalonate was allowed to react with spray-dried potassium fluoride at 120 °C using sulfolane as a solvent, and the formation of diethyl fluoromalonate in ~70% yield was observed by ^{19}F nmr spectrum. preparation of fluoromalonic ester by the chlorine-fluorine exchange using usual calcine-dired potassium fluoride was reported before, but the yield described was poor (25 - 30%).[5]

On the other hand, a high catalytic effect of a fluoride ion on a base-catalyzed condensation such as Knoevenagel reaction is well known,[6,7] and the "spray-dried" potassium fluoride was expected also to have an enhanced effect on these kinds of reactions. Therefore we allowed diethyl fluoromalonate formed in sulfolane in situ as mentioned above to react with aldehydes or ketones. As a result, the condensation forming α-fluoro-α,β-unsaturated esters was actually observed.



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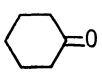
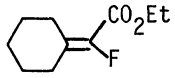
Calcine-dried potassium fluoride gave only a trace of 1 under the same conditions and "freeze-dried"

potassium fluoride was not efficient in this reaction as it has no fluorinating ability.[2)]

Based on these results, it is evident that the "spray-dried" potassium fluoride has greatly enhanced effect both on the halogen-exchange fluorination and on the base-catalized condensation reaction. The present procedure provides a one-pot synthetic method for α-fluoro-α,β-unsaturated esters, a versatile building block for monofluoro organic molecules (Table 1).

Table 1 Preparation of α-fluoro-α,β-unsaturated esters

RCHO or RCOR'	Product[a)]	Yield (%)	Bp (^{o}C/mmHg)[e)]	E/Z[b)] ratio	IR (cm^{-1}) C=O
C_6H_5CHO	$C_6H_5CH=CFCO_2Et$	68	121-123/8 (132-134/13)[c)]	4/96	1735
$CH_3(CH_2)_2CHO$	$CH_3(CH_2)_2CH=CFCO_2Et$	63	68-70/12 (71-73/12)[c)]	12/88	1730
$(CH_3)_2CHCH_2CHO$	$(CH_3)_2CHCH_2CH=CFCO_2Et$	63	84-86/25 (70-72/20)[c)]	14/86	1725
$CH_3CH=CHCHO$	$CH_3CH=CHCH=CFCO_2Et$	54	66-68/15[d)]	8/92	1730
$CH_3(CH_2)_2CH=CHCHO$	$CH_3(CH_2)_2CH=CHCH=CFCO_2Et$	58	81-83/26[d)]	9/91	1730
		52	116-118/10[d)]		1735
$C_6H_5COCH_3$	$C_6H_5(CH_3)C=CFCO_2Et$	58	116-118/3[d)]	7/93	1730

a) Structures were confirmed by means of spectral data. b) Stereochemistry was determined from the relative intensities of ^{19}F nmr signals. c) E. Elkik, Bull. Chem. Soc. Fr., 1964, 2258.
d) New compound: The microanalysis was in satisfactory agreement to the calculated value.
e) 1 mmHg = 133.3 Pa

As a typical example, a heterogeneous mixture of diethyl chloromalonate (1.95 g, 10 mmol) and "spray-dried" potassium fluoride (3.00 g, 50 mmol) in sulfolane (30 ml) was stirred for 3 h at 100 - 120 ^{o}C, and then benzaldehyde (1.60 g, 15 mmol) was added into the reaction mixture. After 10 h of stirring at that temperature, the reaction mixture was poured into water and an oily material was extracted with diethyl ether. After removal of the solvent, the residue was subjected to distillation affording β-fluorocinnamate in 58% (1.13 g) yield, bp 121 - 123 ^{o}C/8 mmHg. ^{19}F nmr ($CDCl_3$): δ 50.2 (*Z*), 34.5 (*E*) ppm from ext. CF_3CO_2H. ^{1}H nmr ($CDCl_3$): δ 6.86 (*Z*, J_{H-F} = 34 Hz), 6.53 (*E*, J_{H-F} = 2 Hz).

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