

Laboratory and industrial synthesis of remifentanil

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Abstract: The submitted review aims at critical evaluation of known synthetic procedures utilized both for laboratory and industrial production of the synthetic analgesic – remifentanil as to their simplicity, published yield and atom economy.

Keywords: remifentanil, synthesis, analgesics

Introduction

Remifentanil – systematic name methyl ester of the 3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]propanoic acid (**1**) – is a synthetic analgesic, marketed, as a hydrochloride, by GlaxoSmithKline, Ganval, Belgium under the trade name of Ultiva®. It belongs to the fast onset, ultra short to long acting analgesics, used as co-analgesics for safe management of general anesthesia during surgery, for management of post-surgery situations or for treatment of hyperalgesia (increased sensitivity to pain) (Guntz et al., 2005). In the human blood remifentanil is metabolized by non-specific blood esterases to essentially inactive metabolite of carboxylic acid. (Feldman et al., 1991). Metabolic half-time in human blood reaches from 10 to 20 minutes (Amin et al., 1995). Remifentanil, its preparation and properties were first published in 1990 (EP0383579, Glaxo Wellcome Inc. (Fig. 1)

Synthetic approaches to remifentanil

The primary reference (EP0383579) describes the preparation of remifentanil by derivatization of the starting piperidone. The synthetic pathway,

designed from the outset for the preparation of remifentanil starts from the commercially available N-benzylpiperidin-4-one (**2**) (WO0140184A2). (Scheme 1)

In its first step Strecker synthesis is used to introduce N-phenylamine and nitrile group, both in the position 4 of the heterocyclic skeleton. Acylated N-phenylamine group can also be found in the structure of target remifentanil. The nitrile group in the molecule (**3**) conveniently serves as a precursor to the carboxylic group. In its paper Kiricojević observed a significant acceleration of the Strecker reaction by the use of mixed dichloromethane/acetic acid solvent, explaining the effect by the better solubility of the *in situ* generated hydrogen cyanide as compared to pure acetic acid (Kiricojević et al., 2002). The hydrolysis of nitrile (**3**) proceeds in two steps involving an amide (**4**), mainly to avoid the formation of nonreactive and insoluble sulfate (**4**). The liberation of free base is followed by acid (HCl) hydrolysis of the amide (**4**) (Scheme 1). Amide (**4**) can also be hydrolyzed in basic conditions by the system KOH/propane-1,2-diol/18-crown-6. It would be tempting to “improve” the two-step transformation of nitrile (**3**) to acid (**5**) by a one-pot reaction

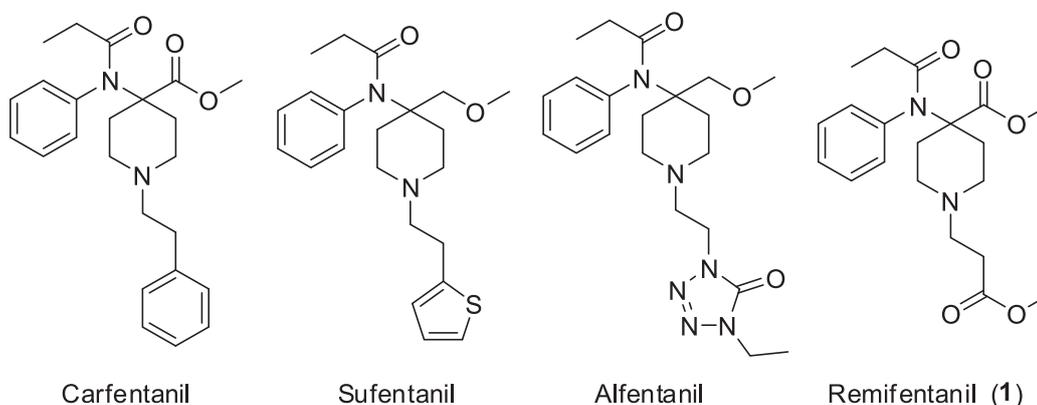
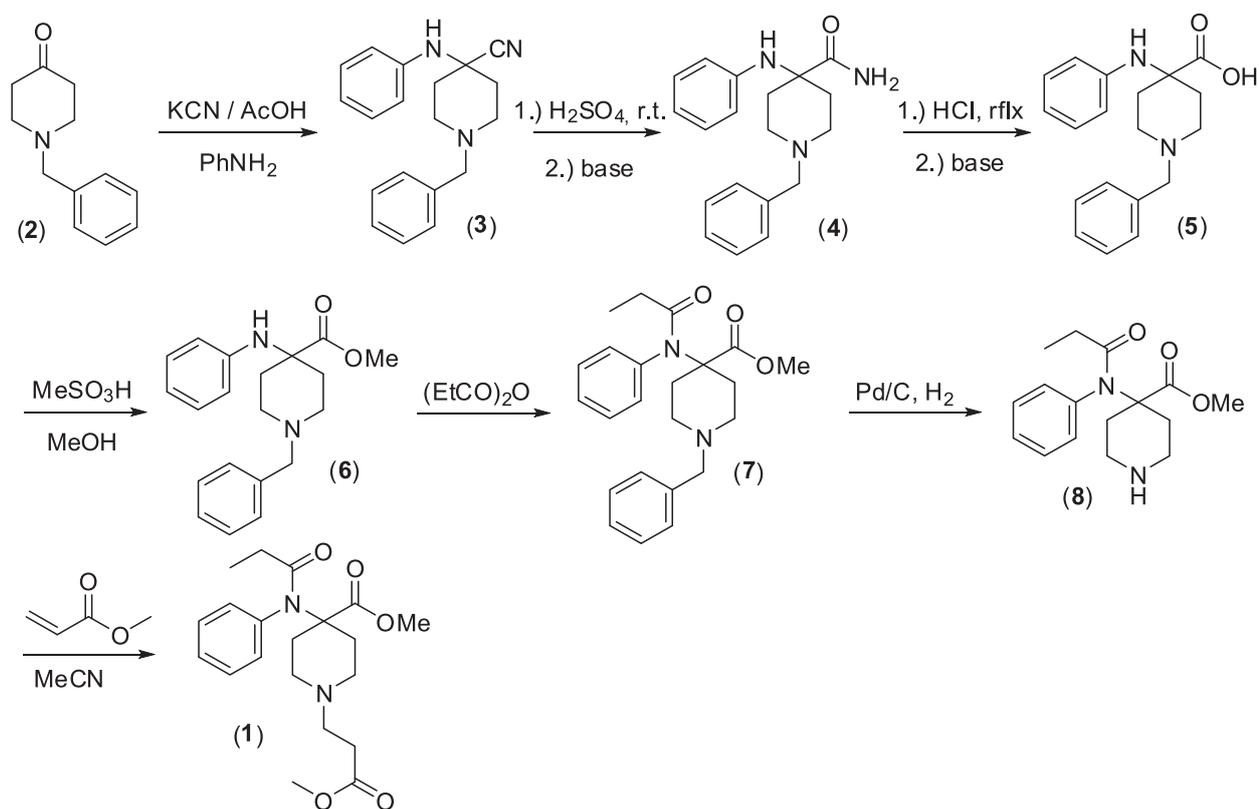
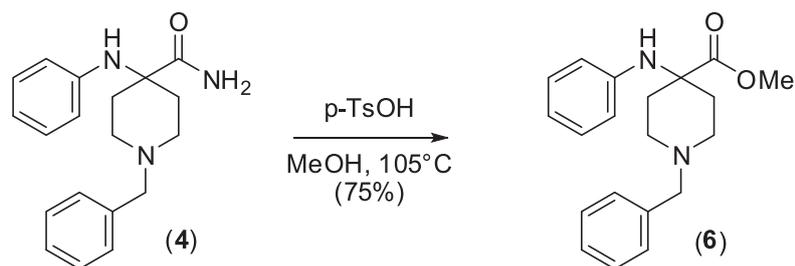


Fig. 1. Remifentanil and its analogs.



Scheme 1.



Scheme 2.

in acidic conditions. Moreover, by judicious choice of solvent one could arrive directly at the methyl ester of the acid, i.e. the intermediate (6). In spite of numerous attempts (Kiricojević et al., 2002) the direct, one step transformation of intermediate (3) to carboxylic acid (5) could not be achieved in acceptable yields. Attempts at basic hydrolysis of the nitrile functionality led to the products of markedly faster retro-Strecker reaction (analogy of the Bruylant decyanization of amines (Kudzma, et al., 1988)) (Kiricojević et al., 2002; Feldman et al., 1990; Marco et al., 1999)).

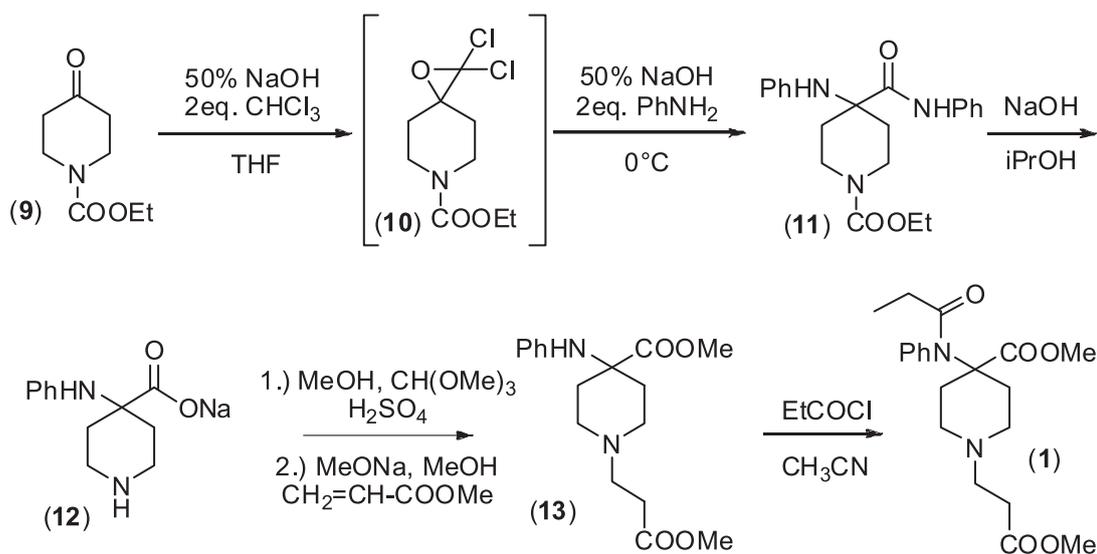
Nevertheless Taber suggested a slight modification of the synthetic sequence and its shortening by one step. In its paper he describes a direct hydrolysis of amide (4) to the methyl ester (6) in good (75 %) yield. Although it would clearly simplify the sequence, no known industrial production of remifentanyl has

adopted this variation of hydrolysis (Taber et al., 1992). (Scheme 2)

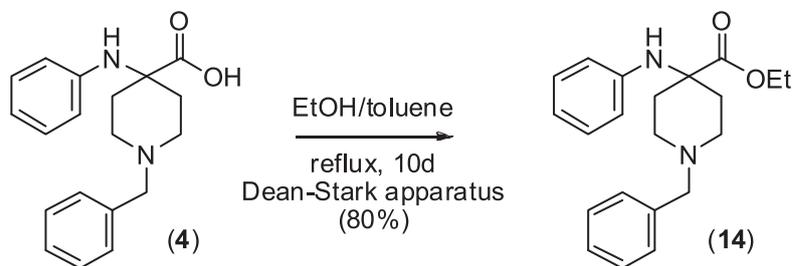
Because of costly safety considerations involving work with toxic hydrogen cyanide, created *in situ* during the Strecker synthesis, an alternative route to 4,4-disubstituted piperidine has been developed, starting from the piperidone (9). (Scheme 3)

In its first step it involves in place of nitrile the intermediate formation of ethyl ester of 4-phenylamino-4-phenylcarbamoylpiperidinecarboxylic acid (11), known from several syntheses of related derivatives. (WO0140184A2)

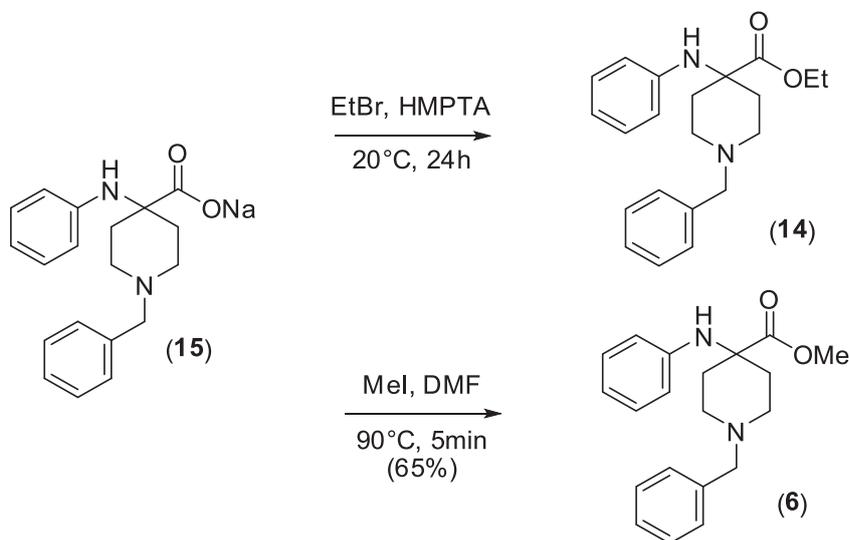
Another seemingly simple synthetic step, but one which made quite a few synthetic teams sweat, was the formation of the important intermediate ester (6) within the original synthetic plan. (Scheme 1) Apart from preparation of the ester from amide (4), which is not used commercially (Scheme 2), preparation of



Scheme 3.



Scheme 4.

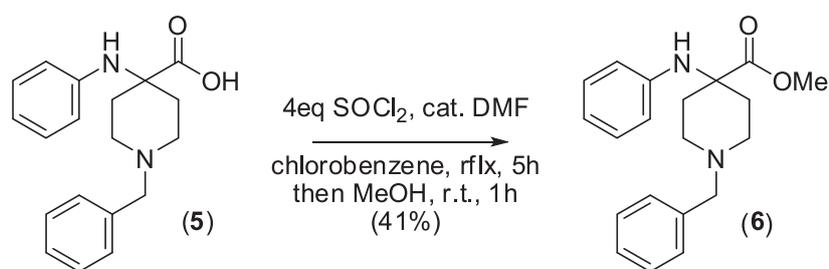


Scheme 5.

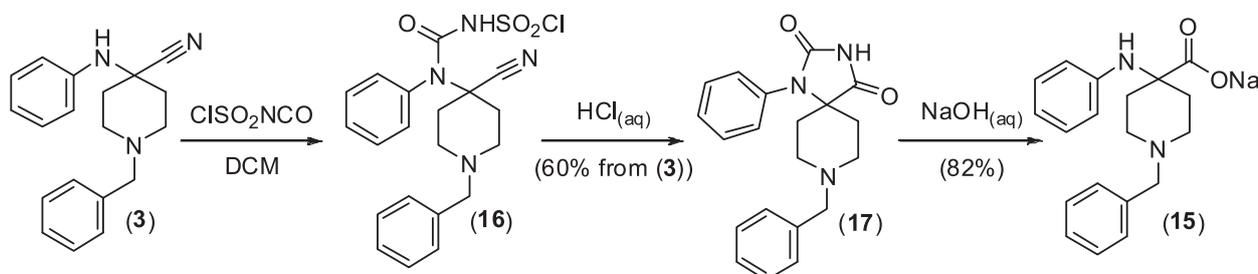
ester requires the acid (5), or its salt. Several papers describe especially the acid (5) as a hard to isolate and purify compound, which is preferably converted to its alkaline salt (Na, K, etc.). Esterification in acidic conditions represents an equilibrium reaction which, in order to achieve acceptable yields, requires long reaction time, high temperature and possibly further

modification of reaction conditions. (Colapret et al., 1989) (Scheme 4)

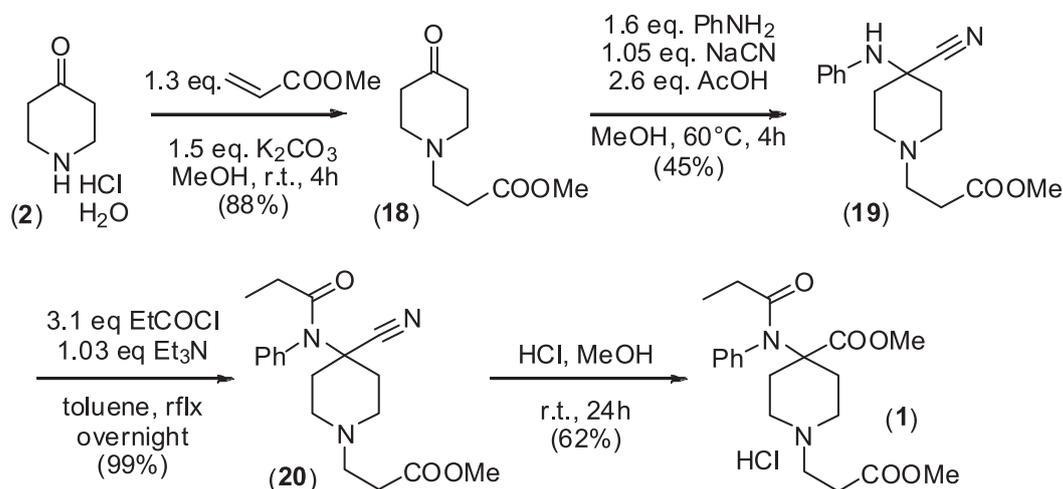
The reaction of the sodium salt of acid (15) with an alkyl halide proceeds in good yield in hexamethylphosphotriamide – HMPTA (Scheme 5) (Van Parys et al., 1981); the yield plummets to an average one (58 %), when dimethylformamide is used (Feld-



Scheme 6.



Scheme 7.



Scheme 8.

man et al., 1990). Higher proportion of alkylating agent leads to partial alkylation at nitrogen atom, or affords a mixture of products. (Scheme 5)

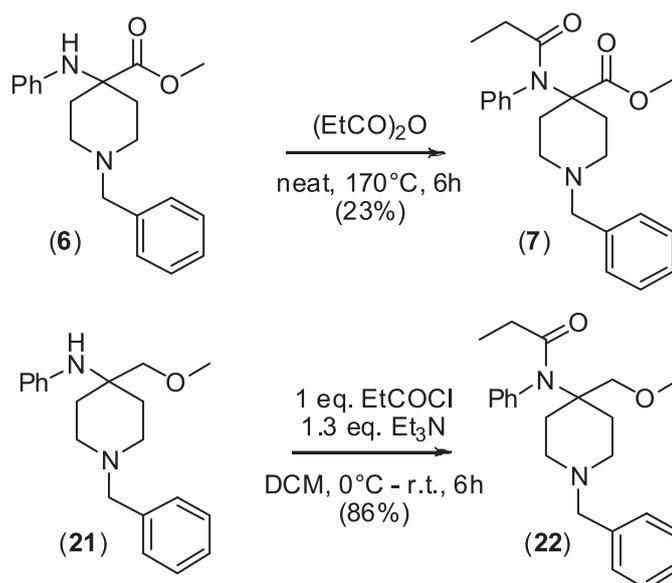
Activation of carboxylic acid by its conversion to chloride proved difficult, probably for steric reasons. This is why Kiricojević, trying this approach to ester (6) only got low yield (41 %) in spite of severe reaction conditions (Scheme 6) (Kiricojević et al., 2002).

Feldman too described an alternative method of transformation of the nitrile (3) to the sodium carboxylate (5), based on utilization of chlorosulfonyl isocyanate for the preparation of spirohydantoin (17) as an intermediate (Scheme 7) (Feldman et al., 1990). However, derivative (17) was obtained only in average yield due to partial conversion of the carbamoylsulfonyl chloride (16) to nitrile (3),

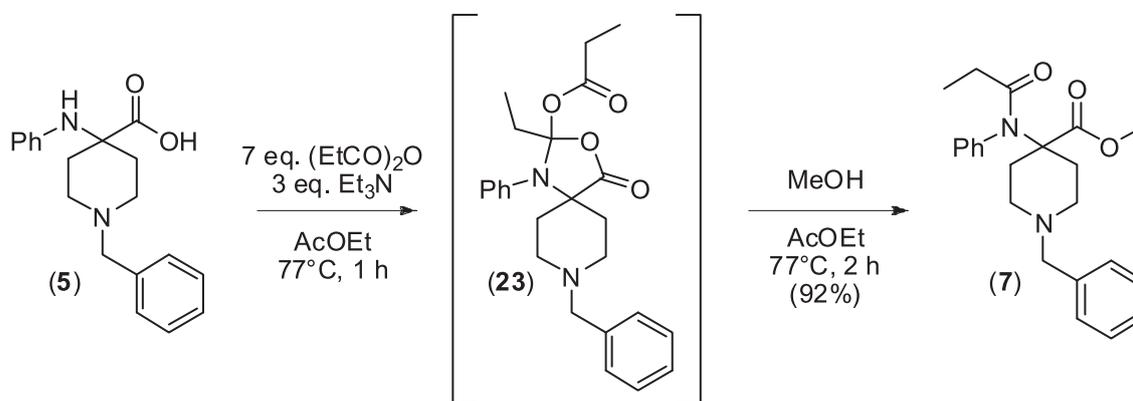
accompanying its further decomposition to the product of retro-Strecker reaction – the piperidone (2). The principal drawback of this approach is the high stability of the spirohydantoin (17), making the preparation of sodium salt (15) energetically demanding.

Scheme 1 through 3 depicts preparations of remifentanil requiring protection of the piperidine nitrogen. In 2006 an alternative procedure has been patented, one starting from the piperidine-4-one (2) (or its hydrochloride) (Scheme 8) (EP1867635A1), and affording the target remifentanil (1) in 4 steps and 24 % overall yield. In this case authors achieved in the final step a direct conversion of nitrile to methyl ester in good yield (62 %).

Literature search (Reaxys, Scifinder) disclosed a solventless propionylation of the anilide nitrogen in



Scheme 9.



Scheme 10.

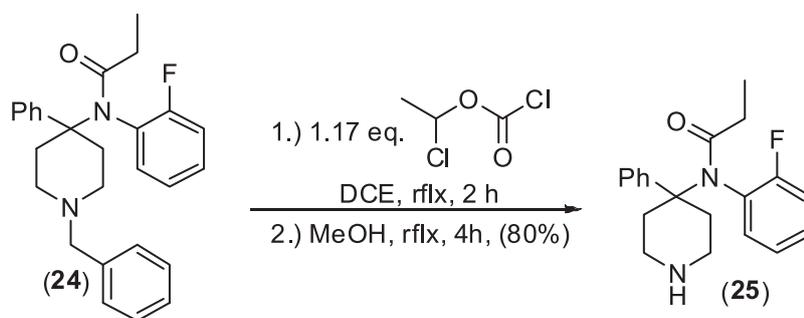
substrate (6) by exclusive use of a high excess of propionic anhydride at 170 °C. Nevertheless, the yields of this transformation are either rather low (23 %, Henriksen et al., 2005), (34 %, US201099880A1) or not given at all (US3998834 A1, US4179569A1). A comparison with analogous propionylations of substrates leading to norsufentanyl or closely related derivatives leads one to the conclusion that lower reactivity of the anilide nitrogen in the substrate (6) is probably due to the proximity of the sterically demanding methoxycarbonyl group. (Srimurugan et al., 2009) (Scheme 9)

According to Kiricojević the ester (6) failed to react with propionyl chloride in DCM even after several days of reflux. In chlorobenzene at temperature elevated to 100–120 °C a significant part of the substrate decomposed, as was the case during reflux in neat propionic anhydride. Conversely, at low temperature the reactivity of propionic anhydride does not suffice for successful propionylation. An addition of bases on the other hand, either pyridine

or DMAP led to complex reaction mixtures. In the end acceptable yields of the acylated product (7) were obtained by use of propionyl chloride (3 eq.) in dichloroethane (80 °C, 4–5 h), to which triethylamine was gradually added (1 eq.). The product was isolated in the form of mono-oxalate salt in the yields of 70–80 %. (Kiricojević et al., 2002)

In 1999 Coleman solved the problem of low nucleophilicity of the secondary amine nitrogen in an elegant way. He let react the amino acid (5) with excess propionic anhydride in the presence of triethylamine, whereby the *in situ* generated spirocyclic intermediate (23) underwent a ring opening by methanol to the intermediate (7) in very good yield. (Scheme 10) (Coleman et al., 1999)

The debenzoylation of ester (7) was carried out in the conditions of catalytic hydrogenation with metals – Pd and/or Pd(OH)₂ (Scheme 1, Table 1). Another potentially applicable debenzoylation uses 1-chloroethyl chloroformate, i.e. transformation of compounds (24) to (25), as has been repeatedly

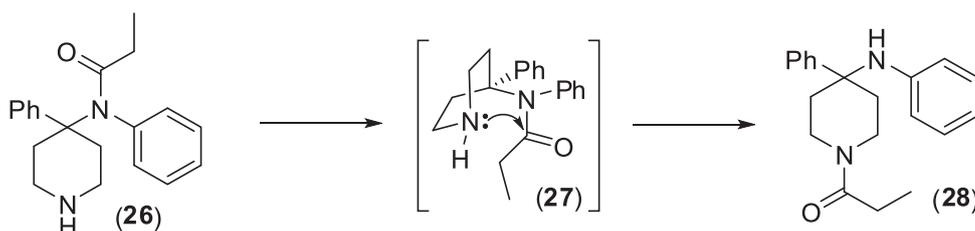


Scheme 11.

Tab. 1. Debenzylation of substrate (7)

	Catalytic system	Solvent	p (H ₂) [atm]	t [h]	T [°C]	Y [%]	Ref.
1	15 % wt. Pd/C(10 %)	MeOH	atm	-	r.t.	85	US3998834A1
2	20 % wt. Pd/C(5 %)	MeOH/EtCOOMe/AcOH 60:2:1	atm	over-night	50	50 ^a	US201099880A1
3	30 % wt. Pd/C(10 %)	EtOH	atm	24	r.t.	52	Henriksen et al., 2005
4	20 % wt. Pd/C(10 %)/ Pd(OH) ₂ /C(10 %)	MeOH	4	12	r.t.	92	Srimurugan et al., 2009
5	1:1	AcOH/H ₂ O 2:3	3–4	3–4	20	95	Kiricojević et al., 2002

a) GC conversion



Scheme 12.

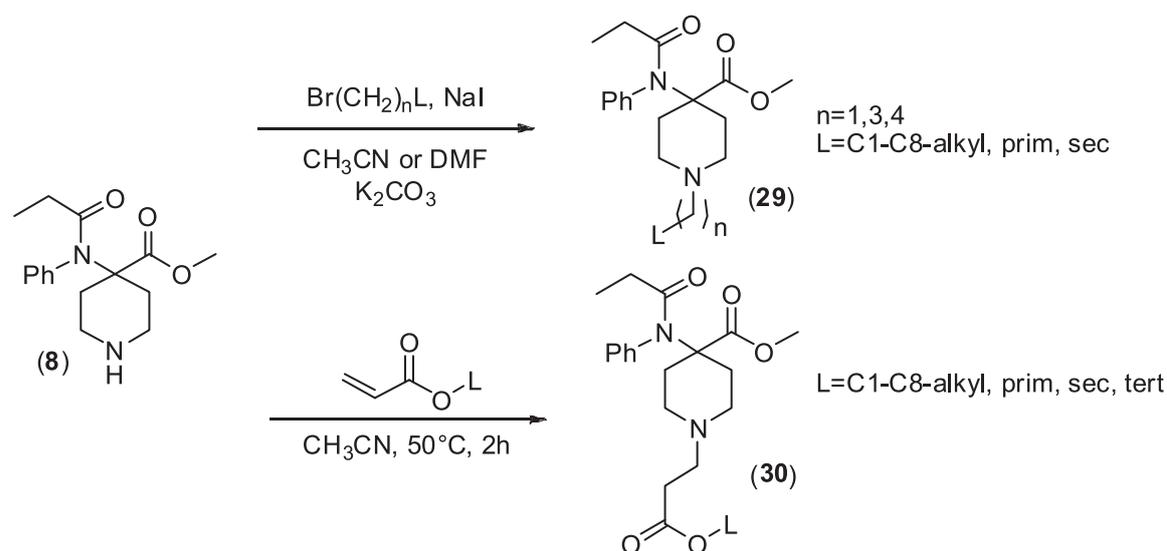
demonstrated on analogous substrates. (Scheme 11) (Kudzma et al., 1988)

It should not be forgotten though that debenzylation involves an intramolecular acyl migration, specifically that of propionyl from aniline nitrogen (26) via (27) to piperidine nitrogen (28). (Scheme 12) (Kudzma et al, 1988, Colapret et al. 1989). This undesirable process can largely be eliminated by speedy workup of the product of debenzylation on the one hand, and by selection of effective and fast debenzylation conditions on the other.

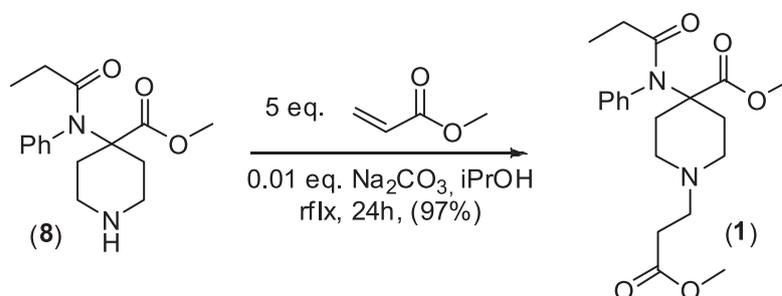
There are several ways to carry out final alkylation of the piperidine ring, the most common one being the Michael reaction at the double bond of methyl acrylate, or nucleophilic substitution by various alkyl halides or alcohols. This was how the series of N-substituted derivatives of piperidine (29) and (30) were prepared. (Scheme 13) (Feldman et al., 1990)

The introduction of methoxycarbonyl ethyl group into the remifentanil molecule is done exclusively by the Michael addition. Numerous experiments were required to select reaction conditions (Scheme 14) leading to formation of the final product (1) in high yield and high purity (over 99 %), followed by the removal of remifentanil (1) from reaction medium by simple filtration. (US2011144346A1)

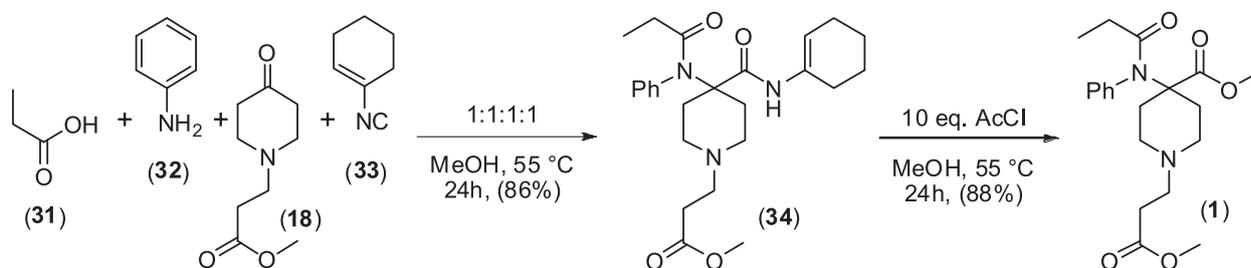
Another synthetic strategy leading to remifentanil is based on the Ugi reaction. Malaquin and co-workers applied Ugi reaction to the preparation of remifentanil in 2010. (Scheme 15)(Malaquin et al., 2010). Its big advantage lies in the effectiveness of the synthetic sequence (3 steps starting from commercially available compounds), one equivalent Ugi procedure (no excess required) and good yield. To be specific, mixing of equimolar amounts of propionic acid (31), aniline (32), piperidone (18) and cyclohexenylisocyanide (33) gives rise to the interme-



Scheme 13.



Scheme 14.



Scheme 15.

diate (34) which, after simple transformation amide to methyl ester afforded the final remifentanyl (1) in 75 % overall yield. From the viewpoint of industrial manufacturing the drawback of the published method is the use of chromatographic methods for product purification.

Acknowledgement

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