

MICHAEL ADDITION OF NITROALKANES TO ALLYL NITRILE DERIVATIVE: SYNTHESIS OF 1,2,3-TRIFUNCTIONALIZED CYCLOPENTANES

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(Reçu le 12 Décembre 2013, Accepté le 19 Février 2014)

ABSTRACT: An efficient conjugate addition of carbon nucleophiles such as nitronate salts to ethyl 5-cyanocyclopent-1-enecarboxylate **3**, produces a variety of 1,2,3-trifunctionalized cyclopentanes **4** in satisfactory yields.

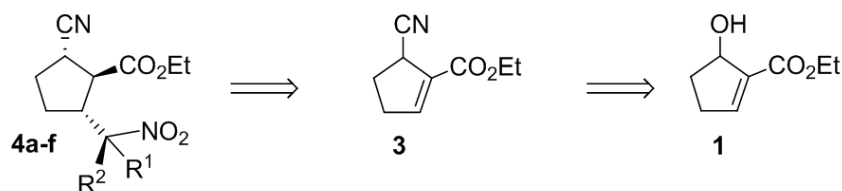
Keywords: Cyclic Baylis-Hillman adducts, DABCO, allyl nitrile, Michael addition, nitroalkanes, 1,2,3-trifunctionalized cyclopentanes.

RÉSUMÉ: L'addition conjuguée de nucléophiles carbonés tels que les sels de nitroalcanes sur le 5-cyanocyclopent-1-énecarboxylate d'éthyle **3**, conduit à une variété de cyclopentanes 1,2,3-trifonctionnalisés **4** avec des rendements satisfaisants.

1. INTRODUCTION

There are several natural or unnatural cyclopentenyl-containing molecules with remarkable biological activity. Such derivatives can be found in alkaloids [1], chokols [2], prostaglandins [3], triquinanes [4], indans [5,6] and guaianes [7]. Therefore, the development of expedient and efficient methods for the construction of such compounds would be being an active area of research. Probably, the most used strategies to prepare complex molecules that possess functionalized cyclopentyl unit were reported for Nazarov cyclization [8], Diels-Alder reaction [9] and for other reaction pathways [10-12].

Furthermore, the Michael addition plays an important role among the numerous asymmetric carbon-carbon bonds forming reactions [13-15]. This represents one of the most elegant and attractive ways to introduce chirality into some Michael acceptors such as allyl nitrile **3**. Particularly interesting challenge is the asymmetric conjugate addition of a carbon nucleophile to electrophilic acceptors which constitutes a very useful synthetic procedure for the preparation of chiral cyclic compounds [16] with vicinal stereogenic centers in a single step. In this area, we report here a convenient synthesis of 1,2,3-trifunctionalized cyclopentane rings **4a-f** via the conjugate addition of nitroalkanes to the prepared cyclic allyl nitrile **3** (Scheme 1).

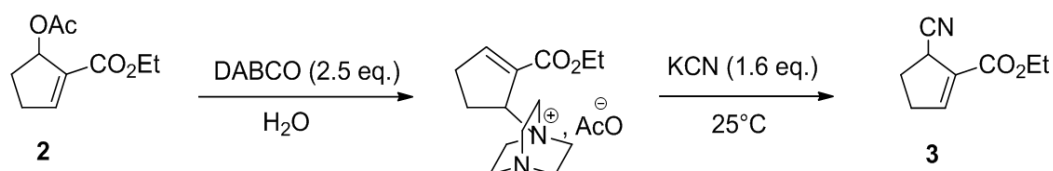


Scheme 1. Retrosynthetic strategy for obtaining 1,2,3-trisubstituted cyclopentanes **4a-f**

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2. RESULTS AND DISCUSSION

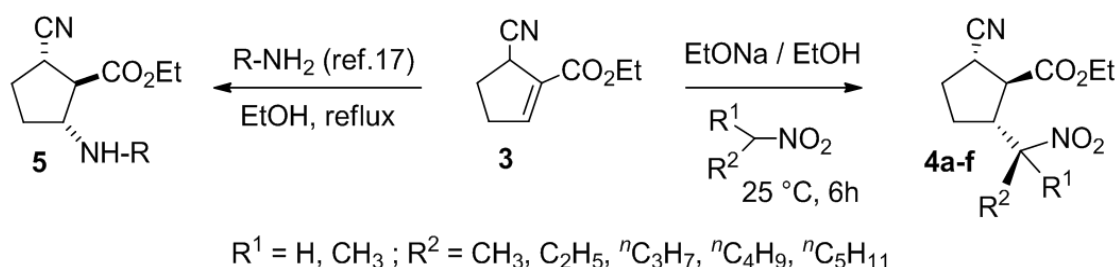
As part of the research program related to the development of synthetic methods for the construction of cyclopentenic skeletons, we are interested in the nucleophilic substitution reaction of the allyl acetate **2** using first, the DABCO as a co-nucleophilic reagent in water through formation of a quaternary ammonium salt which transformed to the corresponding allyl nitrile **3** [17] in the presence of potassium cyanide in a 69% yield (Scheme 2).



Scheme 2. Synthesis of functionalized allyl Nitrile **3**

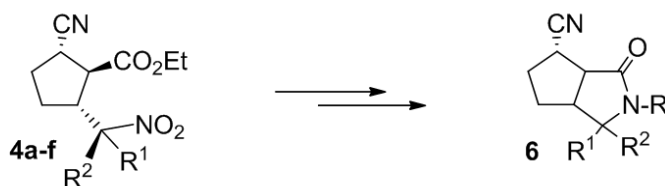
The coupling reaction of nitroalkane anions to electron-poor alkenes is a very powerful synthetic tool for generation of a variety of important targets such as cyclopentenones [18], spiroketals [19], lactones [20,21], furans [22], pyrroles [23] and aromatic derivatives [24]. On the other hand, the Michael addition reaction has performed in the presence of a large variety of bases, both in homogeneous solutions and in heterogeneous catalysis. Weak bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) [25,26], 1,1,3,3-tetramethylguanidine (TMG) [27,28], triphenylphosphine [29] and aqueous sodium hydroxide [30-32] are able to promote the nucleophilic addition using aliphatic nitronate anions, which can react with different electrophiles to give polyfunctionalized products [33]. In this context, we show that the Michael reaction performed on allylic systems of type **3** is very promising with the use of a variety of aliphatic nitroalkanes. Deprotonation of the latter carried out in the presence of sodium ethoxide prepared *in situ* at room temperature to provide **4a-f** in satisfactory yields (48-70%).

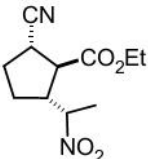
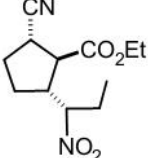
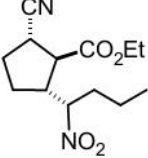
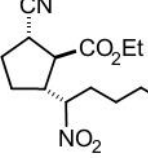
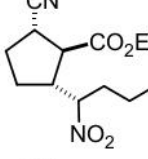
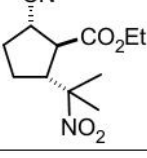
It should be noted here that adducts **4a-f** containing more than one stereogenic center may exist as a mixture of diastereoisomers which is difficult to separate by conventional chromatographic techniques. However, it would be possible to consider similar results we obtained recently from the Michael addition of primary amines on the same allyl nitrile **3** leading to *trans-trans* products **5** [17]. The duplication of signals in ^{13}C NMR of all carbon atoms of nitro adducts **4a-f** are mainly due to the presence of two *trans-trans* diastereoisomers relevant to the asymmetry of exocyclic center (Scheme 3, Table 1).



Scheme 3. Michael addition of nitroalkanes to allyl nitrile **3**

The Michael adducts **4a-f** could be used as starting materials in the synthesis of more complex molecules. The selective reduction of the nitro group [34,35] offers the possibility to access a variety of bicyclic γ -lactams **6** [36,37] will interest biological activities. This work is currently under study (Scheme 4).

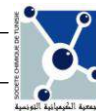

Scheme 4. 1,2,3-Trisubstituted cyclopentanes **4a-f** as source of fused bicyclic γ -lactams **6**
Table 1: Synthesis of 1,2,3-trifunctionalized cyclopentanes **4a-f**

Entry	R ¹	R ²	Product 4	Yield*(%)
a	H	CH ₃		70
b	H	C ₂ H ₅		65
c	H	<i>n</i> C ₃ H ₇		55
d	H	<i>n</i> C ₄ H ₉		50
e	H	<i>n</i> C ₅ H ₁₁		48
f	CH ₃	CH ₃		60

* Yields referred to the pure isolated products characterized by ¹H and ¹³C NMR

3. CONCLUSION

We developed an expedient synthesis of trifunctionalized cyclopentanes **4a-f** from an efficient coupling reaction of cyclic allyl nitrile **3** and nitroalkane salts in absolute ethanol as solvent. The simplicity of this method and its mild reaction conditions seem to be an invaluable way to produce highly functionalized compounds with several stereogenic centers that can serve as useful intermediates for interesting synthetic purposes.



4. EXPERIMENTAL

All reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under dry nitrogen atmosphere with magnetic stirring. All reactions were monitored by TLC on silica gel plates (Fluka Kieselgel 60 F254). Crude products were purified using column chromatography on silica gel (Fluka Kieselgel 70-230 mesh). ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 300 spectrometer at 300 and 75 MHz for ^1H and ^{13}C , respectively in CDCl_3 as solvent and TMS as the internal standard. The chemical shifts (δ) and coupling constants (J) are expressed in parts per million (ppm) and Hertz (Hz), respectively. All NMR spectra were acquired at room temperature. Multiplicity of peaks is indicated by: s: singlet; d: doublet; t: triplet; q: quartet; qt: quintuplet; sept: septuplet; m: multiplet.

4.1. General procedure for the synthesis of 1,2,3-trifunctionalized cyclopentanes 4a,a'-f,f'

A mixture of absolute EtOH (30 mL) and Na (0.41 g, 18 mmol) was allowed to stir under nitrogen. The nitroalkane (18 mmol) and ethyl 5-cyanocyclopent-1-enecarboxylate **3** (1g, 6 mmol) were then added at room temperature and the mixture was stirred for 6 h at 25 °C. The solvent was evaporated under reduced pressure and the residue was then hydrolyzed by a saturated solution of NH_4Cl . After extraction with diethyl ether (5x30 mL), the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate (MgSO_4) and the solvent was evaporated in vacuo. The crude product was purified by column chromatography (silica gel, EtOAc / hexane, 3:7) to afford the corresponding γ -nitro esters **4**.

4.1.1. Ethyl 2-cyano-5-(1-nitroethyl)cyclopentanecarboxylate 4a,a'. Yield: 70% as a yellow liquid; ^1H NMR (CDCl_3 , δ ppm, J Hz): 4.24, 4.19 (2q, 4H, $J = 7.00$), 4.06 (qt, 1H, $J = 6.00$), 3.54-3.45 (m, 2H), 3.19, 3.10 (2t, 2H, $J = 7.00$), 2.33-2.14 (m, 2H), 1.96-1.89 (m, 4H), 1.84-1.35 (m, 4H), 1.32, 1.30 (2d, 6H, $J = 7.00$), 1.20, 1.09 (2t, 3H, $J = 7.00$); ^{13}C NMR (CDCl_3 , δ ppm): 171.8, 169.2 (C=O), 122.2, 121.4 (C \equiv N), 83.0, 80.9 (CH- NO_2), 64.9, 64.6 (OCH $_2$), 61.6, 61.1 (HC-CO $_2$ Et), 55.2, 55.0 (CH-CH- NO_2), 33.4, 31.2 (CH $_2$ -CH-CN), 29.9, 29.3 (CH $_2$ -CH $_2$), 28.0, 27.9 (CH-CN), 15.2, 15.2 (CH $_3$ -CH- NO_2), 14.2, 14.2 (CH $_3$).

4.1.2. Ethyl 2-cyano-5-(1-nitropropyl)cyclopentanecarboxylate 4b,b'. Yield: 65% as a yellow liquid; ^1H NMR (CDCl_3 , δ ppm, J Hz): 4.22, 4.07 (2q, 4H, $J = 7.00$), 3.54-3.32 (m, 2H), 3.18-3.08 (m, 2H), 2.78 (t, 1H, $J = 9.00$), 2.34-2.28 (m, 2H), 2.17-1.95 (m, 4H), 1.92-1.89 (m, 4H), 1.84-1.35 (m, 4H), 1.31, 1.27 (2t, 6H, $J = 6.00$); 1.19, 1.09 (2t, 6H, $J = 9.00$); ^{13}C NMR (CDCl_3 , δ ppm): 170.7, 169.2 (C=O), 122.3, 121.4 (C \equiv N), 83.0, 80.9 (CH- NO_2), 64.9, 64.6 (OCH $_2$), 61.4, 61.1 (HC-CO $_2$ Et), 55.2, 55.0 (CH-CH- NO_2), 32.7, 32.6 (CH $_2$ -CH-CN), 30.7, 30.5 (CH $_2$ -CH $_2$), 29.9, 29.2 (CH $_2$ -CH- NO_2), 28.0, 27.9 (CH-CN), 15.2, 15.1 (CH $_3$ -CH $_2$ O), 14.1, 14.0 (CH $_3$).

4.1.3. Ethyl 2-cyano-5-(1-nitrobutyl)cyclopentanecarboxylate 4c,c'. Yield: 55% as a yellow liquid; ^1H NMR (CDCl_3 , δ ppm, J Hz): 4.25, 4.18 (2q, 4H, $J = 7.00$), 3.41, 3.37 (2q, 2H, $J = 7.00$), 3.18-3.08 (m, 2H), 2.88-2.77 (m, 2H), 2.07-1.94 (m, 6H), 1.67-1.59 (m, 4H), 1.40-1.20 (m, 8H), 1.19, 1.13 (2t, 6H, $J = 6.00$), 0.90, 0.81 (2t, 3H, $J = 7.00$); ^{13}C NMR (CDCl_3 , δ ppm): 171.6, 170.9 (C=O), 120.4, 119.2 (C \equiv N), 89.6, 89.3 (CH- NO_2), 65.8 (OCH $_2$), 62.1, 62.0 (HC-CO $_2$ Et), 46.2, 46.0 (CH $_2$ -CH- NO_2), 43.7, 43.7 (CH-CH- NO_2), 31.9, 31.5 (CH $_2$ -CH-CN), 29.8, 29.7 (CH $_2$ -CH $_2$), 27.6, 25.6 (CH $_2$ -CH $_2$ -CH $_3$), 19.2, 19.1 (CH-CN), 15.2 (CH $_3$ -CH $_2$ O), 14.1, 13.7 (CH $_3$ -CH $_2$).

4.1.4. Ethyl 2-cyano-5-(1-nitropentyl)cyclopentanecarboxylate 4d,d'. Yield: 50% as a yellow liquid; ^1H NMR (CDCl_3 , δ ppm, J Hz): 4.28, 4.19 (2q, 4H, $J = 7.00$), 3.21, 3.16 (2q, 2H, $J = 7.00$), 3.24-3.13 (m, 2H), 2.91-2.85 (m, 2H), 2.78 (q, 1H, $J = 7.00$), 2.15-1.96 (m, 6H), 1.84-1.72 (m, 8H), 1.36-1.29 (m, 14H), 0.93 (2t, 6H, $J = 7.00$); ^{13}C NMR (CDCl_3 , δ ppm): 171.6, 170.6 (C=O), 120.5, 119.3 (C \equiv N), 90.6, 89.8 (CH- NO_2), 62.1, 62.0 (OCH $_2$), 50.7, 49.7 (HC-CO $_2$ Et), 46.3, 46.1 (CH $_2$ -CH- NO_2), 43.9 (CH $_2$ -CH $_2$ -CH $_2$), 32.7, 32.6 (CH-CH- NO_2), 31.8, 31.6 (CH $_2$ -CH-CN), 30.1, 29.9 (CH $_2$ -CH $_2$), 28.0, 27.9 (CH $_2$ -CH $_2$ -CH $_3$), 22.0 (CH-CN), 14.1, 14.1 (CH $_3$ -CH $_2$ O), 13.9, 13.7 (CH $_3$ -CH $_2$).

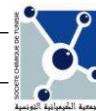
4.1.5. Ethyl 2-cyano-5-(1-nitrohexyl)cyclopentanecarboxylate 4e,e'. Yield: 48% as a yellow liquid; ^1H NMR (CDCl_3 , δ ppm, J Hz): 4.25, 4.20 (2q, 4H, $J = 7.00$), 3.24, 3.17 (2q, 2H, $J = 7.00$), 3.25-3.13 (m, 2H),

2.92-2.82 (m, 2H), 2.78, 2.75 (2t, 2H, $J = 6.00$), 2.15-1.94 (m, 6H), 1.83-1.71 (m, 4H), 1.38-1.26 (m, 22H), 0.90, 0.89 (2t, 6H, $J = 6.00$); ^{13}C NMR (CDCl_3 , δ ppm): 171.7, 170.6 (C=O), 120.5, 119.3 (C \equiv N), 90.6, 89.8 (CH-NO $_2$), 62.1, 62.0 (OCH $_2$), 50.8, 49.0 (HC-CO $_2$ Et), 46.3, 46.1 (H $_2$ C-CH $_2$ -CH $_3$), 44.0 (CH $_2$ -CH-NO $_2$), 32.7, 32.6 (CH-CH-NO $_2$), 31.9, 31.8 (O $_2$ N-CH-CH $_2$ -CH $_2$), 31.6, 31.4 (CH $_2$ -CH-CN), 29.9, 29.3 (CH $_2$ -CH $_2$), 28.9, 27.8 (CH $_2$ -CH $_2$ -CH $_3$), 22.0, 21.9 (CH-CN), 14.1, 14.1 (CH $_3$ -CH $_2$ O), 13.9, 13.8 (CH $_3$ -CH $_2$).

4.1.6. Ethyl 2-cyano-5-(2-nitropropan-2-yl)cyclopentanecarboxylate 4f,f'. Yield: 60% as a yellow liquid; ^1H NMR (CDCl_3 , δ ppm, J Hz): 4.24, 4.19 (2q, 4H, $J = 6.00$), 3.58-3.01 (m, 2H), 2.79 (t, 2H, $J = 9.00$), 2.21-2.11 (m, 2H), 1.99-1.91 (m, 4H), 1.83-1.75 (m, 4H), 1.74 (s, 6H), 1.20, 1.10 (2t, 6H, $J = 6.00$); ^{13}C NMR (CDCl_3 , δ ppm): 171.9, 169.2 (C=O), 122.3, 121.4 (C \equiv N), 83.0, 80.9 (CH-NO $_2$), 65.0, 64.6 (OCH $_2$), 61.7, 61.6 (HC-C-NO $_2$), 55.2, 55.0 (HC-CO $_2$ Et), 36.6 (CH $_2$ -CH-CN), 30.7, 29.2 (C(CH $_3$) $_2$), 28.0, 27.9 (CH $_2$ -CH-NO $_2$), 23.1, 22.2 (CH-CN), 15.1, 14.2 (CH $_3$).

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