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Transesterification of Methyl 2-Nitroacetate to Superior Esters

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In memory of Armida Turchi on the 100th anniversary of her birth

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Abstract: Methyl 2-nitroacetate and methyl acetoacetate have in common the presence of an electron-withdrawing substituent geminal to the methyl ester function but the well-known ease of thermal transesterification of methyl acetoacetate has not been found in methyl nitroacetate. The latter gives uncatalysed thermal transesterification only in low yield and at a temperature higher than that of methyl acetoacetate. Comparative experiments provided further insight into the reactions; protic and Lewis acid catalysts promoted the smooth exchange of the alkanoyl groups, observing first the transesterification of methyl 2-nitroacetate with ethanol, already proved difficult to proceed. Dibutyltin(IV)oxide (DBTO) catalyst offered the spur to set up a convenient synthetic methodology from methyl 2-nitroacetate, encompassing higher molecular weight and functionalised alcohols: aliphatic, unsaturated and oxidation sensitive species were suited to react, delivering the corresponding 2-nitroacetate esters in good yields in most cases.

Introduction

Methyl 2-nitroacetate (**1c**) and ethyl 2-nitroacetate (**4a**) are the almost exclusive representatives of the 2-nitroacetates, receiving considerable attention within the chemical community:[1] their synthesis and reactivity being studied systematically since the nineteenth century.[2-4] Owing to their 1,3-dipole nature and acidity (pK_a ~ 5.8), 2-nitroacetates are involved in useful processes with electrophiles (Knoevenagel condensations/nitroaldol condensation[5,6], conjugated addition,[7] Mannich reaction,[8] cyclopropanations[9], alkylations[10]) and dipolarophiles (as good precursors of dipole intermediates in cycloadditions[11]). Thus interesting molecular structures result, α-amino esters[12], α-keto esters[13], γ-oxo acids[14] as well as isoxazole derivatives[15]. These latter ones are quite popular heterocycles in drug discovery[16] and the reductive cleavage of their weak N-O bond is also a practical tool to direct the insertion of either amino or carbonyl groups on structures downstream.[17] Nitroacetates with different ester moieties would be a valuable precursor of fused isoxazole rings using intramolecular cycloadditions[18,19] and useful building blocks in drug development as several properties of potential candidates would be examined and eventually refined around the ester function[20]. Finally, the opportunity to vary the ester group on nitroacetates would contribute to the design of appropriate synthetic strategies, based on the concept of orthogonal protecting groups[21]. Therefore, an easy and reliable protocol for the synthesis of nitroacetates is desirable, to achieve building blocks with tuned reactivity and stability and additional elements of diversity at the trailing ester function.

Primary 2-nitroacetates can be made by esterification of nitroacetic acid [Eq. (1)][22] or nitration of precursors such as β-ketoesters[23] or α-halo acetates[24]; to the best of our knowledge, their preparation by transesterification with alcohols of either methyl 2-nitroacetate (**1c**) or ethyl 2-nitroacetate (**4a**) has not been addressed systematically and only few reports account for its exploitation, to synthesise purposely tailored compounds.[25,26] Recently, an improved preparation of methyl nitroacetate (**1c**), which solves some of the drawbacks of a previous two step procedure published in the seventies[27], has been reported by Sabatini and co-workers [Eq. (2)][28]. This new procedure allows the preparation of methyl 2-nitroacetate (**1c**) in a convenient and economical way,[29] making it attractive for chemical development. Therefore, **1c** is an attractive compound for a rapid entry into superior esters by transesterification, which often requires acid, basic or metal catalysts.[30, 31] Here we wish to describe the general features of the thermal and catalysed transesterification of **1c**, privileging dibutyltin(IV)oxide (DBTO)[32] over other catalysts [Eq. (3)].[33]

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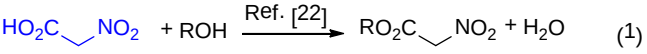

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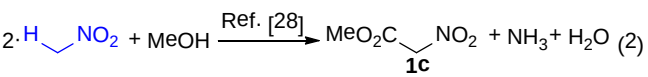

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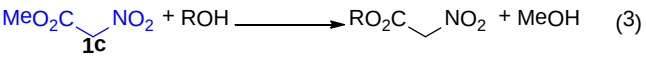

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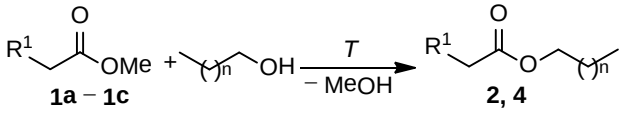
Results and Discussion

It is well known that α,α'-unsubstituted β-keto esters easily undergo transesterification with alcohols without the need of a catalyst;[34-38] on the contrary transesterification of non enolisable α,α'-disubstituted β-keto esters or alkanoyl esters does not take place. This observation suggests that transesterification of β-keto esters is facilitated by the electron-withdrawing (EW) character of the carbonyl in geminal position to the ester group.

The origin of the latter could be attributed to their enol character and the reaction was supposed to precede *via* an acetylketene intermediate.[39,40] Primary nitro compounds bearing an EW substituent in a geminal position, show similar tautomerism, (nitro – aci) as the acidity of the methylenic protons is enhanced.[41,42]

Table 1. Comparative transesterification of methyl esters with 1-alkanols at various temperatures.



1a – 1c **2, 4**

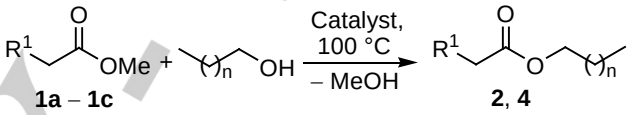
Entry[a]	R^1	n	*T* °C	Conv. (%)[b],[d]	Yield (%)[c],[d]	
1	^{n}Pr, **1a**	6	100	0	**2a**	0
2		6	130	0	**2a**	0
3	Ac, **1b**	6	100	72(48)	**2b**	70(32)
4		0	100	62	**2c**	64
5		6	110	73(62)	**2b**	69(62)
6	NO_2, **1c**	6	100	10(0)	**4d**	10(0)
7		0	100	3	**4a**	0
8		6	110	23(17)	**4d**	7(7)
9		6	120	65(19)	**4d**	10(10)
10		6	130	73(45)	**4d**	6(17)

[a] Reagents and conditions: methyl ester, 1-alkanol (3 equiv.) in a sealed, tube for 24 h. See Experimental section for details. [b] Conversion determined by ^{1}H NMR with the use of an internal standard. [c] Spectroscopic yield determined by ^{1}H NMR with the use of an internal standard. [d] In parentheses conversion/spectroscopic yield after 6 hours.

This evidence lead us to envisage favourable conditions for the alkanoyl exchange during transesterification on **1c** in the absence of catalyst. Preliminary experiments with 1-octanol and ethanol under similar solvent free experimental conditions described by Bader,[35] were carried out in sealed tubes at the indicated temperature without removing methanol at equilibrium (Table 1). This protocol allowed the effective evaluation of the different reactivity among methyl esters **1a**, **1b** and **1c**, despite of the inevitable underestimation of the processes' conversion data. Methyl valerate (**1a**) did not undergo alcoholysis with 1-octanol, even when the temperature was raised up to 130 °C (Table 1, entries 1 and 2). As expected, thermal alcoholysis of acetoacetate **1b** at 100 °C showed good conversion (72 %, Table 1, entry 3) which did not increase significantly at 110 °C (73 %, Table 1, entry 5). No processes other than transesterification were observed, as spectroscopic yields matched conversions (about 70 %, Table 1, entries 3 and 5). Experiments with Methyl 2-nitroacetate (**1c**) revealed a temperature dependent conversion, being close to those carried out on **1a** at 100 °C (10%, Table 1, entry 6) and **1b** at 130 °C (73%, Table 1, entry 10). However, the low yields recorded for those experiments (Table 1, entries 6 and 8 to 10) did suggest degradation processes had taken places. Results on **1c** could not be reproduced when replacing 1-octanol with lower boiling point alcohols: transesterification at 100 °C was not observed with ethanol (Table 1, entry 7), confirming the threshold temperature limit for this process. Thus, the catalysed transesterification of methyl 2-nitroacetate (**1c**) was studied in comparison with that on an inactivated (*i.e.*, **1a**) and activated ester species (*i.e.*, **1b**): both in the presence of ethanol and 1-octanol (Table 2).

Experiments were carried out in the presence of 8 mol% of catalyst with respect to the methyl esters at 100 °C for a fixed time of 90 minutes. Some of the most widely used catalyst for transesterification were selected, belonging to different categories: acids [*p*-toluensulphonic acid, (*p*-TsOH)], bases [4-dimethylaminopyridine, (DMAP)] and transition metal derivatives [dibutyltin oxide (DBTO), titanium (IV) isopropoxide and indium(III) iodide]. DBTO proved more effective on **1c** (Table 2, entry 4) than on **1a** and **1b** (Table 2, entries 1 and 2): both in terms of process conversion and yield.

Table 2. Screening of catalysts.



1a – 1c **2, 4**

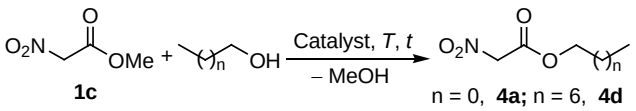
Entry[a]	R^1	n	Catalyst	Conv. (%)[b]	Yield (%)[c]	
1	^{n}Pr	6	DBTO	63	**2a**	39
2	Ac	6	DBTO	77	**2b**	71
3	NO_2	6	*p*-TsOH	82	**4d**	69
4	NO_2	6	DBTO	89	**4d**	64
5	NO_2	6	$Ti(O^iPr)_4$	93	**4d**	84
6	NO_2	6	InI_3	40	**4d**	39
7	NO_2	6	DMAP	100	**4d**	0
8	NO_2	0	*p*-TsOH	81	**4a**	69
9	NO_2	0	DBTO	90	**4a**	50
10	NO_2	0	$Ti(O^iPr)_4$	88	**4a**	69

[a] Reagents and conditions: methyl 2-nitroacetate, alcohol (3 equiv.), catalyst (0.08 equiv) in a sealed tube, at 100 ° C, for 90 min. See Experimental section for details. [b] Conversion determined by ^{1}H NMR with the use of an internal standard. [c] Spectroscopic yield determined by ^{1}H NMR with the use of an internal standard.

Nevertheless, DBTO differed only slightly from, *p*-TsOH and $Ti(O^iPr)_4$, leading to comparable yields of the desired ester products; however, when $Ti(O^iPr)_4$ was used, traces of **4f** were observed deriving from the action of the catalyst. InI_3 provided the octyl ester of **1c** only in a modest 40% yield (Table 2, entry 6). On the other hand, DMAP was unreliable for the transesterification of **1c**, despite of its well-known property to catalyse the transesterification of β-keto esters[43]: only products of polymerisation were observed (Table 2, entry 7).[44] In addition, other side events could be unambiguously perceived when those catalysts operated on methyl esters **1a – 1c**, since a

general mismatch between process conversions and spectroscopic yields was evident.

Table 3. Screening of Catalysts and Reaction Conditions.

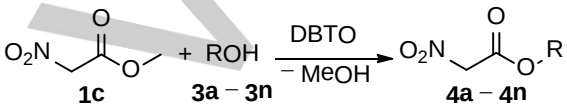


Entry[a]	n	Catalyst [b]	*T* °C	*t* h	Conv. (%)[c]	Yield (%)[d]
1	6	DBTO (5)	30	72	33	18
2	6	$Ti(O^iPr)_4$ (4)	30	72	40	28
3	6	DBTO (4)	60	1.5	31	24
4	6	$Ti(O^iPr)_4$ (4)	60	1.5	27	23
5	6	*p*-TsOH (4)	60	1.5	16	10
6	0	DBTO (5)	100	1.5	87	73
7	6	DBTO (4)	100	1.5	93	77
8	0	*p*-TsOH (5)	100	2+2	95	59
9[e]	0	DBTO (5)	100	4	98	72
10[e]	6	DBTO (4)	100	0.75+0.75	100	86
11	0	DBTO (5)	100	1+1	99	92
12	0	*p*-TsOH (5)	100	1+1	87	74
13	0	$Ti(O^iPr)_4$ (5)	100	1+1	99	88
14	0	DBTO (5)	100	2+2	99	73
15	0	*p*-TsOH (5)	100	2+2	97	72

[a] Reagents and conditions: methyl 2-nitroacetate, alcohol (3 equiv.), catalyst (0.04-0.05 equiv) in a sealed tube. See Experimental section for details. [b] In parentheses catalyst loading (mol %). [c] Conversion determined by ^{1}H NMR with the use of an internal standard. [d] Spectroscopic yield determined by ^{1}H NMR with the use of an internal standard. [e] Heated in a microwave reactor (150 W).

Thus, a series of experiments were designed around the most effective catalysts, to understand and overcome those issues: temperature and reaction time as well as catalyst loading were taken into consideration as process variables (Table 3). Transesterefication slows down significantly when decreasing the temperature, providing very low yields (Table 3, entries 1 – 5), as typically proven by DBTO at 60 °C: a significant difference between conversion and product yield (31 % *vs* 24 %) was unquestionable. Further decrease in temperature to 30 °C demanded longer time to the process to reach the same yields: after 72 hours the yields resulted in 18% with a conversion of 33%. (Table 3, entry 1). Better results, in terms of yields and reduced mismatch between conversion and yield were obtained lowering the catalyst load. Utilising 4 % mol of DBTO yields moved up from 50 % to 73 % (Table 3 entry 6 *vs* Table 2 entry 9) and 64 % to 79% (Table 3 entry 6 vs Table 2 entry 4). Conducting the experiments in a microwave reactor does not lead to significant improvements (Table 3, entry 9 *vs* entry 6). Moisture containing reagents could be assumed to favour hydrolysis of the esters back to nitroacetic acid, which is sensitive towards the release of carbon dioxide at a temperature higher than 70 °C. Then nitromethane and methanol were observed in the ^{1}H NMR spectra of the crude reaction mixture. (see Table S1, supporting information). A number of experiments have been carried out using various alcohols, to understand the effect of water on the yield of the transesterification process (Table S1, entries 1 - 12, supporting information). The results of these experiments show that appropriate anhydrification of the alcohol is crucial to limit the amount of the nitromethane byproduct up to 10% against nitroacetates **4**. A further decrease in the decomposition of **1c** cannot be achieved because nitroacetate **1c** decomposes even in the absence of alcohol or alcohol and catalyst (Table S1, entries 13 - 14).

Table 4. Transesterification of methyl 2-nitroacetate (**1c**) with various alcohols in the presence of DBTO.



Entry[a]	3	R	4	
			Yield (%)[b]	Yield (%)[c]
1	**a**	CH_3CH_2	61	17[45]
2	**b**	$CH_3(CH_2)_2CH_2$	88	35[46]
3	**c**	$CH_3(CH_2)_4CH_2$	68	-
4	**d**	$CH_3(CH_2)_6CH_2$	69	-
5	**e**	$CH_3(CH_2)_2CHCH_3$	66	-
6	**f**	CH_3CHCH_3	74	92[25d
7	**g**	$BrCH_2CH_2CH_2$	55	75[47]
8	**h**	$C_6H_5CH_2$	67(59)[d]	80[48]
9	**i**	*p*-(CH_3O)-$C_6H_4CH_2$	30	-
10	**j**	$H_2C=CHCH_2$	66	67[49],68[50
11	**k**	$H_2C=CHCH_2CH_2$	59	-
12	**l**	$H_2C=CH(CH_2)_2CH_2$	50	-
13	**m**	$HC\equiv C(CH_2)_2CH_2$	48	-
14	**n**	$ClCH_2(CH_2)_4CH_2$	76	-

[a] All reactions were performed on a 0.5 mmol scale of **1c** using 4 mol % of DBTO, at 100 °C for 1.5 hours [b] Yield of isolated product after chromatography. [c] Yield of esters **4** as reported in literature starting from nitroacetic acid unless otherwise stated. [d] In parentheses the yield on a tenfold scale.

Interestingly, when the process was replicated on **1c** adopting a two-step protocol, (i.e., including a nitrogen gas purge at half time), the conversion peaked up, allowing a fair recovery of product **4a** and **4d** (Table 3, entries 10 – 13). This operation had the benefit to expel methanol out of the mixture and allow the

shift of the esterification-alcoholysis equilibrium towards the desired ester product **4**. The major advantage of this protocol is the easier purification of products as a consequence of the total consumption of the starting methyl esters. However, extending the reaction time for both the DBTO and *p*-TsOH catalysed processes, was disadvantageous: yields dropped considerably in the first case (Table 3, entry 14) whereas no gain was recorded in the second one (Table 3, entry 15), demonstrating the overall lability of esters **4a** and **4d** when kept at 100 °C for long time spells.

Finally, regarding the time to complete the process at 100 °C, a kinetic profile of transesterification of **1c** with 1-octanol was determined. Using a larger excess of 1-octanol (5 equiv) than used for experiments in Table 3 (3 equiv) the kinetic profile showed that the spectroscopic yield reaches a value of about 80 % after twenty-thirty minutes (Figure S1, supporting information). The latter is likely the equilibrium yield in the process.

Useful preparations of nitroacetate esters (Table 4)

Scope and limitations of the catalysed transesterification of **1c** were explored within a wide variety of alcohols **3c** – **3n** under solvent free conditions and in the presence of 4 **–** 5 mol% loading of DBTO; yields of isolated esters **4a – 4n** ranged from moderate to good values depending on alcohol functionalisation or structure (Table 4). Aliphatic alcohols **3a – 3f** were the most adaptable reagents to displace methanol from **1c**, even in the presence of steric hindrance at their β position (pentan-2-ol, Table 4, entry 5) or their α-position as for a secondary alcohol such as *iso*-propanol (**3f)** (Table 4, entry 6). *Tert*-butyl alcohol did not react and the benzyl alcohols suffered from the presence of substituents on the ring: the isolated yield for **3h** was 67 % but in the case of **3i** it dropped to 30 % (Table 4, entries 8 and 9). Modest yield were observed also for the halogenated alcohol 3-bromopropanol (**3g**) (55 %, Table 4, entry 7): but the 6-chlorohexanoyl ester derivative **3n** was isolated in a good 76% yield (Table 4, entry 14). Alkenyl esters **3j** – **3l** were obtained in modest to good yields (entries 10 – 12) and among them, allyl derivative **3j** could be prepared conveniently. In this latter case, yields matched those reported in the literature from the coupling of nitroacetic acid with allyl alcohol; and more importantly Carroll type rearranged products[51] were not detected in the crude reaction mixture, despite of the documented tendency of β-keto allyl esters to lose carbon dioxide *via* the corresponding enol intermediate.

Investigation on 1-pentyn-5-ol (Table 4, entry 13) did confirm the possibility to achieve the corresponding ester derivative **3m**: however, optimisation of the reaction conditions would be required to circumvent the chemical lability of the carbon-carbon triple bond.

Conclusion

Elaboration of methyl 2-nitroacetate (**1c**) *via* transesterification has been demonstrated feasible, expanding the value of this well-known building block for synthetic purposes. Although the activated methylene moiety was thought to favour the alkanoyl group exchange, as for methyl acetoacetate (**1b**), thermal uncatalysed conditions were not suitable for **1c**, which struggled to react. On the other hand, the catalysed transesterification on **1c** showed promising results. In particular DBTO, $Ti(O^iPr)_4$ and *p*-TsOH were the most effective catalysts, even though **1c** was observed to decompose to nitromethane and CO_2 *via* a likely stepwise mechanism involving nitroacetic acid as transient species. Although, this side reaction could prove difficult to avoid, both the reduction of DBTO loading and the optimisation of the process achieved its minimisation and succeeded in the preparation of esters **4a** and **4d**. Conditions were also replicated for the synthesis of a wide range of ester derivatives, making this DBTO catalysed process a practical tool for nitroacetic acid esters preparation: either chemically sensitive or stable alcohols were possible to use, as demonstrated by the synthesis of ester **4j**, which was stable towards rearrangement.

Experimental Section

General Methods: Microwave-assisted reactions were carried out in a CEM Discover™ single-mode microwave reactor with an IR temperature sensor. Melting points were determined in open capillary tubes with a Stuart Scientific SMP3 melting-point apparatus. Chromatographic separations were performed on silica gel 60 (40 – 6.3 μm) with analytical-grade solvents, driven by a positive pressure of air according to the procedure of Still et al.[52] R_f values refer to TLC (visualised with UV light and / or by dipping the plates into a solution of $KMnO_4$ followed by heating with a heat gun) performed on 25 mm silica-gel plates (MerckF254) with the eluant indicated for column chromatography. For gradient column chromatography, the R_f values refer to the more polar eluant unless otherwise stated. The notation PE refers to petrol ether fraction boiling between 40 and 60 °C. Solvents were removed by evaporation with the use of a rotary evaporator at room temperature. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Varian Mercuryplus 400 spectrometer (operating at 400 MHz for ^{1}H and 100.58 MHz for ^{13}C) unless otherwise stated. The ^{1}H NMR spectroscopic data are reported as [multiplicity, coupling constant(s) in Hz, integration]; the multiplicity is denoted by s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, hept = heptet, dq = double quartet, m = multiplet or unresolved. The multiplicities of the ^{13}C NMR signals (s, d, t, q) and the ^{1}H and ^{13}C signals, if possible, were assigned by means of gCOSY, gHSQC, and gHMBC experiments. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$: 7.24 ppm for ^{1}H NMR) and solvent ($CDCl_3$: 77.0 ppm) for ^{13}C NMR. ESI (electrospray ionisation) mass spectra were recorded (infusing the sample solution directly into the ESI chamber by syringe pump) with a ThermoFisher LCQ-Fleet ion-trap instrument, and spectra were recorded by using the ESI^- technique (negative current). EI (electron impact) mass spectra (at ionisation voltage of 70 eV) were obtained by using a Shimadzu QP5050A quadrupole-based mass spectrometer. Ion mass/charge (m/z) ratios are reported as values in atomic mass units followed by the intensities relative to the base peak in parentheses. Infra-red (IR) spectra were recorded with a Perkin Elmer BX FTIR spectrophotometer. Intensity of absorption band is indicated by s = strong, m = medium, w = weak, vw = very weak, br = broad. Elemental analyses were per formed with a Perkin–Elmer 240C Elemental Analyser apparatus or Thermofinnigan CHN-S Flash E1112 analyser. All compounds were named by using Autonom (Beilstein Information Systems) and were modified as appropriate.

Materials: Commercially available alcohols, Dibutyltin(IV) oxide (DBTO) $Ti(O^iPr)_4$, *p*-toluensulphonic acid (PTSA) were used as supplied. InI_3 was generated *in situ* from indium metal and iodine refluxing in the appropriated alcohol[53] Alcohols were stored for 96 h over molecular sieves (3 Å) under nitrogen before use. [54]

General procedure for Tables 1 and 2 (thermal and catalysed transesterifications). A mixture of methyl ester **1a** or **1b** or **1c** (0. 200 –

0.240 mmol), alcohol (ethanol or 1-octanol) (0.600 – 0.720 mmol) and catalyst (only Table 2, 0.016 – 0.0192 mmol) was heated in a sealed tube immersed in a constant temperature oil bath maintained a the indicated temperature. After 90 min (Table 2) or 6 and 24 hours (Table 1) the reaction mixture was cooled and $(CH_3)_2SO_2$ was added (14.0 – 16.0 mg, 0.149 – 0.170 mmol) as internal standard. The mixture was dissolved in $CDCl_3$ and the ^{1}H NMR spectrum was recorded. The conversions and yields are reported in Table 2. Integration of the C*H*$_3$ protons of $(CH_3)_2SO_2$ (δ = 2.93 ppm), C*H*$_2$CO protons for ethyl or octyl esters, were used to calculated the spectroscopic yield. Integration of the C*H*$_3$ protons of internal standard (δ = 2.93 ppm), and the C*H*$_3$O protons of the methyl esters (**1a** – **1c**), were used to calculated the conversion. Both yields and conversions are calculated based on the weighed methyl ester. In a preliminary ^{1}H NMR experiment conducted in $CDCl_3$ using the internal standard [$(CH_3)_2SO_2$] the weighed and spectroscopic determined amounts of methyl esters **1a** – **1c** were compared to validate the procedure.

General procedure for Table 3 (catalysed transesterification). A mixture of methyl ester **1c** (25.2 mg, 0.212 mmol) alcohol (0.636 mmol) and catalyst (0.00848 – 0.0106 mmol) was heated in a sealed tube immersed in a constant temperature oil bath maintained a the indicated temperature. After 6 and 24 hours the reaction mixture was cooled and $(CH_3)_2SO_2$ was added (16.6 mg, 0.212 mmol) as internal standard. The mixture was dissolved in $CDCl_3$ and the ^{1}H NMR spectra was recorded. The conversions and yields are reported in Table 3. Integration of the C*H*$_3$ protons of internal standard, the C*H*$_2$NO$_2$ protons of the **4a** or **4d** nitroacetate esters, were used to calculated the spectroscopic yield. Integration of the C*H*$_3$ protons of internal standard and the C*H*$_3$O protons of **1c**, were used to calculated the conversion. Both yields and conversions are calculated based on the weighed methyl ester.

General procedure for catalysed transesterification of **1c** *with* **3a** – **3n**. (Table 4). A mixture of methyl 2-nitroacetate (**1c**) (50.5 – 66.8 mg, 0.42 – 0.56 mmol), DBTO (4.2 – 5.6 mg, 0.04 equiv) and alcohol (**3a** – **3n**), (1.23 – 1.68 mmol, 5 equiv) was heated in a sealed tube at 100 °C under stirring for 0.75 h. After cooling to 20 °C, the septum was equipped with a long syringe needle (gas inlet) and a short needle (gas outlet) and a moderate stream of nitrogen gas (30 – 35 mL/min) was kept for 10 minutes to allow the purge of methanol, so as not to cause evaporative loss of substrate. The reaction mixture was then heated at 100 °C for additional 0.75 h. The volatiles were removed under reduced pressure and the crude residue was purified by column chromatography on silica gel eluting with the appropriate combination of PE / EtOAc or hexane / EtOAc.

Ethyl 2-nitroacetate (**4a**). Compound **4a** (45.2 mg, 61 %) was obtained as transparent colourless oil from **1c** (66.3 mg). R_f = 0.54 (PE / EtOAc = 5 : 1). ^{1}H NMR ($CDCl_3$): δ = 1.28 (t, 3 H, *J* = 7.0 Hz, C*H*$_3$), 4.27 (t, 2 H, *J* = 7.0 Hz, C*H*$_2$O), 5.13 ppm (s, 2 H, C*H*$_2$NO$_2$). ^{13}C NMR ($CDCl_3$): δ = 13.8 (q, *C*H$_3$), 63.1 (t, *C*H$_2$O), 76.2 (t, CH$_2$NO$_2$), ppm 161.8 (s, *C*O). MS (ESI$^-$, MeOH): *m* / *z* (%) = 132 (100) [*M* – 1]$^-$. IR ($CDCl_3$): nu tilde = 3034 (vw), 2930 (m), 2856 (m), 1755 (s) [C=O], 1568 (s) [NO$_2$], 1335 (m) [NO$_2$], 1215 (m) cm^{-1}. $C_4H_7O_4$ (133.10): calcd. C 36.09, H 5.30, N 10.52; found C 35.84, H 5.60, N 10.16.

***n*-Butyl 2-nitroacetate** (**4b**). Compound **4b** (72.9 mg, 88 %) was obtained as colourless oil from **1c** (61.2 mg). R_f = 0.51 (PE / EtOAc = 15 to 5 : 1). ^{1}H NMR ($CDCl_3$): δ = 0.91 (t, 3 H, *J* = 7.4 Hz, C*H*$_3$), 1.35 (sext, 2 H, *J* = 7.6 Hz C*H*$_2$CH$_3$), 1.60 – 1.68 (m, 2 H, C*H*$_2$CH$_2$O), 4.24 (t, 2 H, *J* = 6.8 Hz, C*H*$_2$O), 5.14 ppm (s, 2 H, C*H*$_2$NO$_2$). ^{13}C NMR ($CDCl_3$): δ = 13.5 (q, *C*H$_3$), 18.8 (t, *C*H$_2$CH$_3$), 30.2 (t, *C*H$_2$), 67.0 (t, *C*H$_2$O), 76.3 (t, *C*H$_2$NO$_2$), ppm 161.9 (s, *C*O). MS (ESI$^-$, MeOH): *m* / *z* (%) = 160 (100) [*M* – 1]$^-$. IR ($CDCl_3$): nu tilde = 3018 (m), 2965 (m), 2963 (w), 2875 (w), 1755 (s) [C=O], 1567 (s) [NO$_2$], 1524 (w), 1428 (w), 1407 (w), 1334 (m) [NO$_2$], 1219 (s) cm^{-1}. $C_6H_{11}NO_4$ (161.158): calcd. C 44.72, H 6.88, N 8.69; found C 44.90, H 6.92, N 8.45.

***n*-Hexyl 2-nitroacetate** (**4c**). Compound **4c** (69.9 mg, 68 %) was obtained from **1c** (64.7 mg) as colourless oil. R_f = 0.63 (PE / EtOAc = 15 to 5 : 1). ^{1}H NMR ($CDCl_3$;): δ = 0.87 (t, 3 H, *J* = 6.8 Hz, C*H*$_3$), 1.22 – 1.38 (m, 6 H, 3 × C*H*$_2$), 1.60 – 1.70 (m, 2 H, C*H*$_2$CH$_2$O), 4.23 (q, 2 H, *J* = 6.8 Hz, C*H*$_2$O), 5.14 ppm (s, 2 H, C*H*$_2$NO$_2$). ^{13}C NMR ($CDCl_3$): δ = 13.9 (q, *C*H$_3$), 22.4 (t, *C*H$_2$), 25.2 (t, *C*H$_2$), 28.2 (t, *C*H$_2$), 31.2 (t, *C*H$_2$), 67.3 (t, *C*H$_2$O), 76.3 (t, CH$_2$NO$_2$), 161.8 ppm (s, *C*O). MS (ESI$^-$, MeOH): *m* / *z* (%) = 188 (100) [*M* – 1]$^-$. IR ($CDCl_3$): nu tilde = 3018 (m), 2961 (w), 2930 (w), 1750 (m), 1710 (s) [C=O], 1568 (m) [NO$_2$], 1432 (m), 1417 (m), 1363 (s), 1216 (s) cm^{-1}. $C_8H_{15}NO_4$ (189.21): calcd. C 50.78, H 7.99, N 7.40; found C 50.77, H 8.37, N 7.96.

Octyl 2-nitroacetate (**4d**). Compound **4d** (64.0 mg, 69 %) was obtained as colourless oil from **1c** (50.8 mg). R_f = 0.21 (Hexane / EtOAc = 30 : 1). ^{1}H NMR ($CDCl_3$): δ = 0.862 (t, 3 H, *J* = 7.2 Hz, C*H*$_3$CH$_2$), 1.19 – 1.38 (m, 10 H, 5 × C*H*$_2$), 1.60 – 1.70 (m, 2 H, C*H*$_2$CH$_2$O), 4.23 (q, 2 H, *J* = 6.8 Hz, C*H*$_2$O), 5.14 ppm (s, 2 H, C*H*$_2$NO$_2$). ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 14.0 (q, *C*H$_3$), 22.6 (t, *C*H$_2$), 25.6 (t, *C*H$_2$), 28.2 (t, *C*H$_2$), 29.0 (t, *C*H$_2$), 29.1 (t, *C*H$_2$), 31.7 (t, *C*H$_2$), 67.3 (t, *C*H$_2$O), 76.3 (t, *C*H$_2$NO$_2$), 161.8 ppm (s, *C*O). MS (ESI$^-$, MeOH): *m* / *z* (%) = 216 (100) [*M* – 1]$^-$. IR ($CDCl_3$): nu tilde = 3034 (vw), 2959 (m), 2930 (s), 2857 (m), 1753 (s) [C=O], 1568 (m) [NO$_2$], 1335 (m) [NO$_2$], 1211 (m) cm^{-1}. $C_{10}H_{19}NO_4$ (217.16): calcd. C 55.28, H 8.81, N 6.45; found C 55.68, H 8.92, N 6.24.

***s*-Pentyl 2-nitroacetate** (**4e**). Compound **4e** (48.9 mg, 66 %) was obtained as colourless oil from **1c** (50.5 mg). R_f = 0.44 (Hexane EtOAc = 20 to 5 : 1). ^{1}H NMR ($CDCl_3$): δ = 0.90 (t, *J* = 7.4 Hz, 3 H, C*H*$_3$CH$_2$), 1.26 (d, *J* = 6.4 Hz, 3 H, C*H*$_3$CH), 1.29 – 1.40 (m, 2 H, C*H*$_2$), 1.44 – 1.54 (m, 1 H, C*H*$_2$), 1.57 – 1.67 (m, 1 H, C*H*$_2$), 5.01 – 5.10 (m, 1 H, C*H*CH$_3$), 5.11 ppm (s, 2 H, C*H*$_2$NO$_2$). ^{13}C NMR ($CDCl_3$): δ = 13.7 (q, *C*H$_3$CH$_2$), 18.4 (q, *C*H$_3$CH), 19.6 (t, *C*H$_2$CH$_3$), 37.6 (t, *C*H$_2$CH), 74.8 (d, *C*HO), 76.5 (t, *C*H$_2$NO$_2$), 161.4 ppm (s, *C*O). MS (ESI$^-$, MeOH): *m* / *z* (%) = 174 (100) [*M* – 1]$^-$. IR ($CDCl_3$): nu tilde = 3030 (vw), 2964 (m), 2936 (m), 2874 (w), 1750 (s) [C=O], 1566 (s) [NO$_2$], 1459 (w), 1382 (m), 1355 (m), 1329 (m) [NO$_2$], 1223 (s), 1116 (m). $C_7H_{13}NO_4$ (175.18) calcd.: C, 47.99; H, 7.48; N, 8.00; found C 48.28, H 7.31, N 8.40.

***i*-Propyl 2-nitroacetate** (**4f**). Compound **4f**[55] (60.3 mg, 74 %) was obtained as colourless oil from **1c** (65.6 mg). R_f = 0.37 (PE / EtOAc = 5 : 1). ^{1}H NMR ($CDCl_3$): δ = 1.28 (d, 6 H, *J* = 6.4 Hz, C*H*$_3$), 5.10 (s, 2 H, C*H*$_2$NO$_2$), 5.13 ppm (hept, *J* = 6.4 Hz, 1 H, C*H*(CH$_3$)$_2$). ^{13}C NMR ($CDCl_3$): δ = 21.5 (q, 2 C, 2 × *C*H$_3$), 71.6 (d, *C*HO), 76.5 (t, *C*H$_2$NO$_2$), 161.3 ppm (s, *C*O). MS (ESI$^-$, MeOH): *m* / *z* (%) = 146 (100) [*M* – 1]$^-$. IR ($CDCl_3$): nu tilde = 3031 (vw), 2986 (m), 2938 (w), 1750 (s) [C=O], 1556 (s) [NO$_2$], 1466 (w), 1378 (w), 1327 (w) [NO$_2$], 1274 (m), 1226 (m), 1102 (m) cm^{-1}. $C_5H_9NO_4$ (147.13): calcd. C 40.82, H 6.17, N 9.52; found C 40.39, H 6.97, N 9.89.

3-Bromopropyl 2-nitroacetate (**4g**). Compound **4g** (52.8 mg, 55 %) was obtained as colourless oil from **1c** (51.2 mg). R_f = 0.37 (hexane / EtOAc = 10 to 4 : 1). ^{1}H NMR ($CDCl_3$): δ = 2.22 (qn, 2 H, *J* = 6.4 Hz, C*H*$_2$), 3.43 (t, 2 H, *J* = 6.4 Hz, C*H*$_2$Br), 4.41 (t, 2 H, *J* = 6.4 Hz, C*H*$_2$O), 5.17 ppm (s, 2 H, C*H*$_2$NO$_2$). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.5 (t, CH$_2$Br), 31.1 (t, *C*H$_2$), 64.8 (t, CH$_2$O), 76.1 (t, CH$_2$NO$_2$), 161.5 ppm (s, *C*O). MS (ESI$^-$, MeOH): *m* / *z* (%) = 226 (100) [(M + 2) – H]$^-$, 224 (94) [M – H]$^-$. IR ($CDCl_3$): nu tilde = 3030 (vw), 2970 (w), 2928 (w), 2854 (w), 1762 (m), [C=O], 1569 (s) [NO$_2$], 1374 (w), 1337 (w) [NO$_2$], 1253 (w), 1219 (w), 1200 (w) cm^{-1}. $C_5H_8BrNO_4$ (226.03) calcd.: C, 26.57; H, 3.57; N, 6.20; found C 26.64, H 4.04, N 6.41.

Benzyl 2-nitroacetate (**4h**). Compound **4h** (73.0 mg, 67 %) was obtained from **1c** (66 mg) as low melting solid (lit.[56] m. p. 37 °C). Eluant: PE / EtOAc = 10 to 7.5 : 1. R_f = 0.44 with PE / EtOAc = 5 : 1. ^{1}H NMR ($CDCl_3$): δ = 5.16 (s, 2 H, C*H*$_2$NO$_2$), 5.27 (s, 2 H, C*H*$_2$O), 7.34 – 7.42 ppm (m, 5 H, Ar-H). ^{13}C NMR ($CDCl_3$): δ = 68.6 (t, *C*H$_2$O), 76.1 (t, *C*H$_2$NO$_2$), 133.4 (s, Ar-C), 128.5 (d, Ar-C), 128.7 (d, 2 C, Ar-C), 128,9 (d, 2 C, Ar-C), 161.7 ppm (s, *C*O). MS (EI): *m* / *z* (%): 148 (34) [*M* – NO$_2$]$^+$, 120 (10), 107 (70), 91 (100) [PhCH$_2$]$^+$, 77 (32) [C$_6$H$_5$]$^+$, 51 (25). IR

($CDCl_3$): nu tilde = 3089 (w), 3032 (w), 2930 (w), 2860 (w), 1760 (s) [C=O], 1568 (s) [NO_2], 1496 (w), 1454 (w), 1332 (w) [NO_2], 1271 (w), 1195 (w) cm^{-1}. $C_9H_9NO_4$ (195.175): calcd.: C 55.39, H 4.65, N 7.18; found C 55.11, H 5.04, N 7.03.

Scale-up. Compound **4h** (484 mg, 59 %) was obtained from 500 mg of **1c**. The spectroscopic an analytical data are identical to those obtained above.

4-Methoxybenzyl 2-nitroacetate (**4i**). Compound **4i** (29.6 mg, 30 %) was obtained as colourless oil from **1c** (51.5 mg). R_f = 0.34 (Hexane / EtOAc = 10 to 4 : 1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3 H, C*H*$_3$O), 5.14 (s, 2 H, C*H*$_2$NO$_2$), 5.20 (s, 2 H, C*H*$_2$O), 6.86 – 6.91 (m, 2 H, Ar-H), 7.26 – 7.32 ppm (m, 2 H, Ar-H). ^{13}C NMR (50.28 MHz, $CDCl_3$): δ = 55.3 (q, *C*H$_3$O), 68.7 (t, *C*H$_2$O), 76.2 (t, *C*H$_2$NO$_2$), 114.1 (d, 2 C, Ar-C), 126.1 (s, 1 C, Ar-C), 130.6 (d, 2 C, Ar-C), 160.1 (s, 1 C, Ar-C), 161.6 ppm (s, *C*O). MS (EI): *m / z* (%) = 225 [*M*]$^+$ (13), 179 (2) [*M* – NO_2]$^+$, 121 (100) [$CH_2C_6H_4OMe$]$^+$, 109 (5), 91 (9), 77 (22). IR ($CDCl_3$): nu tilde = 3008 (w), 2961 (w), 2839 (w), 1755 (s) [C=O], 1614 (m), 1568 (m) [NO_2], 1372 (w), 1333 (w) [NO_2], 1250 (w), 1175 (m), 1035 (w) cm^{-1}. $C_{10}H_{11}NO_5$ (225.20) calcd.: C, 53.33; H, 4.92; N, 6.22; found C 53.56, H 4.89, N 6.51.

Allyl 2-nitroacetate (**4j**). Compound **4j**[49] (54.0 mg, 66 %) was obtained as colourless liquid from **1c** (66.8 mg). R_f = 0.47 (PE / EtOAc = 10 to 5 : 1). ^{1}H NMR ($CDCl_3$): δ = 4.72 (dt, *J* =1.2 and 6.0 Hz, 2 H, C*H*$_2$O), 5.17 (s, 2 H, C*H*$_2$NO$_2$), 5.30 (dq, *J* = 1.2 and 10.4 Hz, 1 H, HC=C*H*$_2$), 5.35 (dq, 1 H, *J* = 1.2 and 17.2 Hz, HC=C*H*$_2$), 5.82 – 5.95 ppm (m, 1 H, *H*C=CH$_2$). ^{13}C NMR ($CDCl_3$): δ = 67.3 (t, *C*H$_2$O), 76.2 (t, *C*H$_2$NO$_2$), 120.1 (t, *C*H$_2$=CH), 130.3 (d, *C*H=CH$_2$), 161.5 ppm (s, *C*O). MS (EI) : *m / z* (%) = 99 (< 1) [*M* – NO_2]$^+$, 88 (8) [*M* – $OCH_2CH{=}CH_2$]$^+$, 70 (10), 57 (59) [$OCH_2CH{=}CH_2$]$^+$, 41 (100) [$CH_2CH{=}CH_2$]$^+$. IR ($CDCl_3$): nu tilde = 3090 (w), 3029 (w), 2957 (w), 1758 (s) [C=O], 1566 (s) [NO_2], 1331 (m) [NO_2], 1201 (s) cm^{-1}. $C_5H_7NO_4$ (145.12): calcd. C 41.38, H 4.86, N 9.65; found C 40.93, H 4.23, N 9.62.

3-Butenyl 2-nitroacetate (**4k**). Compound **4k** (51.4 mg, 59 %) was obtained as colourless oil from **1c** (65.4 mg). R_f = 0.56 (PE / EtOAc = 10 to 5 : 1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.37 – 2.50 (m, 2 H, C*H*$_2$CH=CH$_2$), 4.30 (t, 2 H, *J* = 6.7 Hz, C*H*$_2$O), 5.04 – 5.14 (m, 2 H, C*H*$_2$=CH), 5.10 (s, 2 H, C*H*$_2$NO$_2$), 5.62 – 5.84 ppm (m, 1 H, C*H*=CH$_2$). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 32.4 (t, $CH_2CH{=}CH_2$), 65.7 (t, *C*H$_2$O), 76.0 (t, *C*H$_2$NO$_2$), 117.6 (t, *C*H$_2$=CH), 132.8 (d, *C*H=CH$_2$), 161.8 ppm (s, *C*O). MS (ESI$^-$, MeOH): *m / z* (%) = 158 (100) [*M* – H]$^-$. IR ($CDCl_3$): nu tilde = 3084 (w), 3032 (w), 2986 (m), 2931 (w), 1755 (s) [C=O], 1643 (w), 1564 (s) [NO_2], 1458 (w), 1433 (w), 1406 (w), 1375 (m), 1336 (NO_2), 1274 (m), 1207 (m) cm^{-1}.

4-Pentenyl 2-nitroacetate (**4l**). Compound **4l** (47 mg, 50 %) was obtained as clear oil from **1c** (65.2 mg). R_f = 0.64 (PE / EtOAc = 10 to 5 : 1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.72 – 1.86 (m, 2 H, C*H*$_2$CH$_2$), 2.04 – 2.19 (m, 2 H, C*H*$_2$CH=CH$_2$), 4.27 (t, *J* = 6.4 Hz, 2 H, C*H*$_2$O), 4.98 – 5.14 (m, 2 H, C*H*$_2$=CH), 5.14 (s, 2 H, C*H*$_2$NO$_2$), 5.62 – 5.84 ppm (m, 1 H, C*H*=CH$_2$). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 27.3 (t, $CH_2CH_2CH{=}CH_2$), 29.7 (t, *C*H$_2$CH=CH$_2$), 66.4 (t, *C*H$_2$O), 76.3 (t, *C*H$_2$NO$_2$), 115.7 (t, *C*H$_2$=CH), 136.7 (d, *C*H=CH$_2$), 161.7 ppm (s, *C*O). MS (ESI$^-$, MeOH): *m / z* (%) = 172 (100) [*M* – H]$^-$, 171 (75) [*M* – 2]$^-$. IR ($CDCl_3$): nu tilde = 3081 (w), 3030 (w), 2977 (m), 2941 (m), 1755 [C=O], 1641 (m), 1566 (s) [NO_2], 1334 (m) [NO_2], 1269 (m), 1203 (m) cm^{-1}.

4-Pentinyl 2-nitroacetate (**4m**). Compound **4m** (31.9 mg, 48 %) was obtained as colourless oil from **1c** (50.9 mg). R_f = 0.53 (PE / EtOAc = 10 to 2 : 1). ^{1}H NMR ($CDCl_3$): δ = 1.86 – 1.93 (m, 2 H, C*H*$_2$CH$_2$), 1.97 (t, *J* = 2.5 Hz, 1 H, C*H*C), 2.28 (td, *J* = 6.8 and 2.6 Hz, 2 H, C*H*$_2$C), 4.38 (t, *J* = 6.4 Hz, 2 H, C*H*$_2$O), 5.16 ppm (s, 2 H, C*H*$_2$NO$_2$). ^{13}C NMR ($CDCl_3$): δ = 15.0 (d, *C*H$_2$C), 27.0 (t, *C*H$_2$CH$_2$), 65.6 (t, *C*H$_2$O), 69.5 (d, *C*HC), 76.2 (t, *C*H$_2$NO$_2$), 82.2 (s, *C*CH), 161.7 ppm (s, *C*O). MS (ESI$^-$, MeOH): *m / z* (%) = 170 (100) [*M* – H]$^-$. IR ($CDCl_3$): nu tilde = 3307 (m) [≡C-H], 3030 (w), 2967 (w), 2937 (w), 2118 (w) [C≡C], 1757 (s) [C=O], 1568 (s) [NO_2], 1336 (m) [NO_2], 1267 (m), 1218 (m), 1199 (m) cm^{-1}. $C_7H_9NO_4$ (171.15) calcd.: C 49.12, H 5.30, N 8.18; found C 49.15, H 5.17, N 8.43.

6-Chlorohexyl 2-nitroacetate (**4n**). Compound **4n** (73.0 mg, 76 %) was obtained as colourless oil from **1c** (51.2 mg). R_f = 0.22 (Hexane / EtOAc = 10 : 1). ^{1}H NMR ($CDCl_3$): δ = 1.32 – 1.42 (m, 2 H, C*H*$_2$CH$_2$), 1.42 – 1.51 (m, 2 H, C*H*$_2$CH$_2$), 1.64 – 1.72 (m, 2 H, C*H*$_2$CH$_2$O), 1.72 – 1.81 (m, 2 H, C*H*$_2$CH$_2$Cl), 3.52 (t, *J* = 6.4 Hz, 2 H, C*H*$_2$Cl), 4.26 (t, *J* = 6.4 Hz, 2 H, C*H*$_2$O), 5.15 ppm (s, 2 H, C*H*$_2$NO$_2$). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.0 (d, CH_2CH_2), 26.3 (t, CH_2CH_2), 28.1 (t, CH_2CH_2O), 32.3 (t, *C*H$_2$CH$_2$Cl), 44.8 (t, *C*H$_2$Cl), 67.0 (t, *C*H$_2$O), 76.2 (t, *C*H$_2$NO$_2$), 161.8 ppm (s, *C*O). MS (ESI$^-$, MeOH): *m / z* (%) = 224 (36) [*M* + 2 – H]$^-$, 223 (10) [*M* + 1 – H]$^-$, 222 (100) [*M* – H]$^-$. IR ($CDCl_3$): nu tilde = 2941 (w), 2862 (w), 1755 (s) [C=O], 1568 (s) [NO_2], 1336 (m) [NO_2], 1271 (m), 1215 (m), cm^{-1}. $C_8H_{14}ClNO_4$ (223.65) calcd.: C 42.96, H 6.31, N 6.26; found C 42.99, H 6.47, N 6.11.

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