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One-pot N-acylation and N-alkylation of *o*-nitroaniline with saturated hydrocarbons in the presence of carbon monoxide

Irena S. Akhrem,* Dzhul'etta V. Avetisyan, Nikolai D. Kagramanov, Pavel V. Petrovskii and Nadezhda E. Mysova

A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 5085; e-mail: cmoc@ineos.ac.ru

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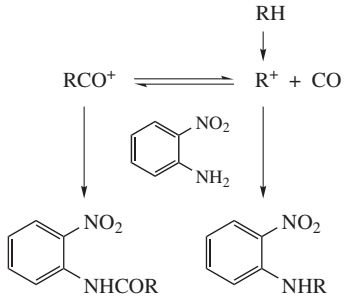
The first one-pot N-acylations and N-alkylations of *o*-nitroaniline with saturated hydrocarbons were performed in the presence of superelectrophiles; the role of CO in the alkylation with *n*-pentane is discussed.

The selective syntheses of fine chemicals directly from alkanes and cycloalkanes is an important problem of current organic chemistry.[1–4]

Here, we report the N-acylation and N-alkylation of *o*-nitroaniline with *n*-pentane, cyclopentane (acylation only), norbornane, trimethylenenorbornane (TMNB) and adamantane (AdH) with or without CO in the presence of $CX_4{\cdot}2AlBr_3$ (X = Br or Cl) superelectrophiles (Scheme 1).

The simple and common methods of N-alkylation of amines with saturated hydrocarbons have not been described. The tosylamination of alkanes and cycloalkanes with tosylimidoiodobenzene, PhI=NTs, as the nitrene source catalyzed by Fe and Mn porphyrins was ineffective and nonselective.[5(a)] More recently, a similar approach with Cu- and, particularly, Ag-based catalysts was found more successful. However, pentane and hexane formed isomeric mixtures of corresponding R–NTs.[5(b)] The synthesis of $Ad'NH_2$ (Ad′ is adamantyl or methyl adamantanes) from Ad′H and NCl_3 in the presence of promoted aluminum halides was described.[6(a),(b)] The Ritter reaction was applied to the preparation of amides from AdH and nitriles in the presence of electrophiles.[7] Recently, a new one-pot synthesis of amides from amines, CO and saturated hydrocarbones has been reported.[8]

Nitroaniline was chosen as a model of a very weak N-nucleophile, although its alkylation and acylation products (particularly, with bi- and tricyclanes) may be interesting by themselves. Aromatic amines are found in biologically natural products, pharmaceuticals, dyes, materials with conductive and emissive properties and ligands for transition-metal-catalyzed reactions.[9] *N*-(1-Adamantyl)-2-nitroaniline is an intermediate in the synthesis of 1,5-benzodiazepine, which is used as a gastrin and cholecystokinin antagonist,[10(a)] while other *N*-adamantyl nitroanilines are promising organic materials for nonlinear optics.[10(b)–(d)] Nitroanilines are valuable precursors of anilines, which are important intermediates in the preparation of dyes, pharmaceuticals, herbicides and pesticides.[9,11]



RH = *n*-pentane, cyclopentane, norbornane, trimethylenenorbornane and adamantane

Scheme 1

Here, the alkylation of nitroaniline with alkanes and cycloalkanes, as well as nitroaniline acylation with *n*-pentane, *endo*-TMNB and AdH, was performed for the first time. The acylation of *o*-nitroaniline with cyclopentane and norbornane has been briefly described previously.[8] To perform acylation, *o*-nitroaniline was added to an *in situ* generated acylium salt from RH and CO in the presence of a superelectrophile $CX_4{\cdot}2AlBr_3$ (X = Br or Cl) in CH_2Br_2 (conditions for the generation of acylium salts were specified elsewhere[8]), and the reactions were carried out in an atmosphere of CO under the conditions shown in Table 1. The structures of the products were proved by ^1H and ^{13}C NMR spectroscopy and mass spectrometry (see Online Supplementary Materials).

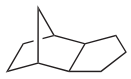
Acylations of *o*-nitroaniline were carried out at temperatures from –20 to +50 °C. The reactions proceeded selectively to furnish a single product in 75–97% yield (with respect to E) for cyclopentane, norbornane and *endo*-TMNB or only 27–30% for pentane and AdH.

Nitroaniline probably enhances the stability of corresponding acylium cations. Even at 35–50 °C, 60–75% yields of acylation products were reached in the reactions of *o*-nitroaniline with RCO^+ generated from norbornane and cyclopentane. On the contrary, in the absence of nitroaniline, the reactions of these cycloalkanes with CO in the presence of $CX_4{\cdot}2AlBr_3$ give carbonyl-containing products in very poor yields, if at all, even at 20 °C. To perform the alkylation, *o*-nitroaniline was added to a reaction mixture containing $CX_4{\cdot}2AlBr_3$ and a saturated hydrocarbon. The alkylation temperature was varied from 0 to 50 °C. The yields of the alkylated products were 67–87%, except for cyclopentane, which did not react at temperatures from –20 to 35 °C.

Note that the previously described adamantylation of nitro-substituted aromatic amines with 1-AdOH in protic acids was shown to proceed inefficiently. For example, the reaction of *o*-nitroaniline with 1-AdOH in H_2SO_4, gave *N*-adamantyl *o*-nitroaniline in ~13–19% yields for five to six days, while in a mixture of H_3PO_4 and AcOH, both N- and C- alkylated products were formed.[6(c)]

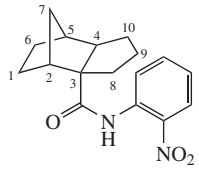
The selectivity and regioselectivity of both alkylation and acylation reactions leading to the formation of the products containing *tert*-pentyl, cyclopentyl, 2-norbornyl and 1-adamantyl groups from *n*-pentane, cyclopentane, norbornane and AdH,

Table 1 Alkylation and acylation of *o*-nitroaniline (**I**) with RH and the {RH + CO} system in the presence of $CBr_4 \cdot 2AlBr_3$ (E) in CH_2Br_2 solution.[a]

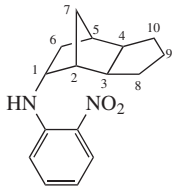
Entry	RH	Conditions for reactions of RCO^+ with **I**				Product yield (% on E)[b]	
		T/°C	*t*/h	[**I**]:[E]	CO	Alkylation product	Acylation product
1	*n*-Pentane	–20	1.5	3:1	+	27	18
2		0	1	1:1	–	0	0
3		20	12	2:1	–	4 (R = Bu) 11 (R = C_5H_{11})	
4		20	12	2:1	+	72	27
5		35	1	2:1	+	87	13
6		–20	1	1:1	+	0	50
7		0	0.5	1:1	–	0	
8		0	4	1:1	–	0	
9		0	2	1:1	+	0	97
10		35	1	1:1	+	0	60
11		0	1	1:1	–	47	
12		0	2	1:1	–	81	
13		35	1	1:1	–	44	
14		35	1	1:1	+	—	75
15		50	1	1:1	+	—	65
16	Adamantane	0	1	1:1	–	75[c]	
17		0	4	2:1	+	35	30
18		0	1	1:1	–	67	
19		0	1	1:1	+		76
20		10	1	1:1	+		62
21		0	2	2:1	–	28[d]	

[a]In entries 13 and 20, E = $CCl_4 \cdot 2AlBr_3$; [E] = 0.87–0.98 mol dm^{-3}, except for entry 15, where [E] = 0.34 mol dm^{-3}. [b]According to GC data. [c]Yield of an isolated product. [d]A mixture of three isomers in a ratio of 1:1.4:2.7.

respectively, is obviously due to a highly preferable formation of a single carbocationic species and the respective acylium cation from these substrates under the employed conditions (similar to the reported reactions[4]). An entirely different behaviour was observed for TMNB. According to the previously reported data,[4(a),12] the exclusive formation of *exo* isomer **1** was observed in case of *o*-nitroaniline acylation. On the contrary, *exo* isomer **2** was the product of *o*-nitroaniline alkylation. Under optimal conditions (Table 1), both **1** and **2** were formed selectively.



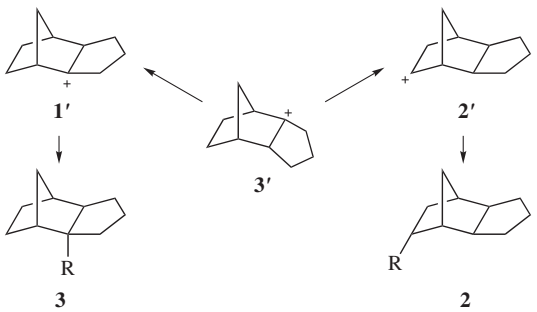
1



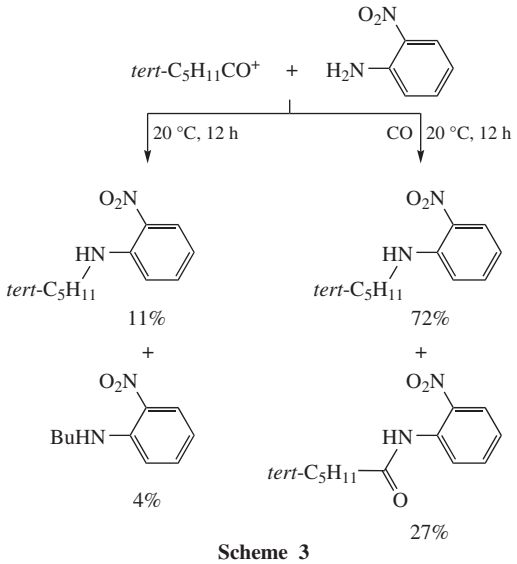
2

The order of stability for trimethylenenorbornyl cations was reported[13] to be **3′** > **1′** >> **2′** (Scheme 3).

Thus, it should be expected that more stable tertiary cation **1′** rather than secondary one **2′** would be accumulated in the reaction medium; therefore, alkylation product **3** rather than isomer **2** (R = $NHC_6H_4NO_2$) should be produced. Note that a



Scheme 2



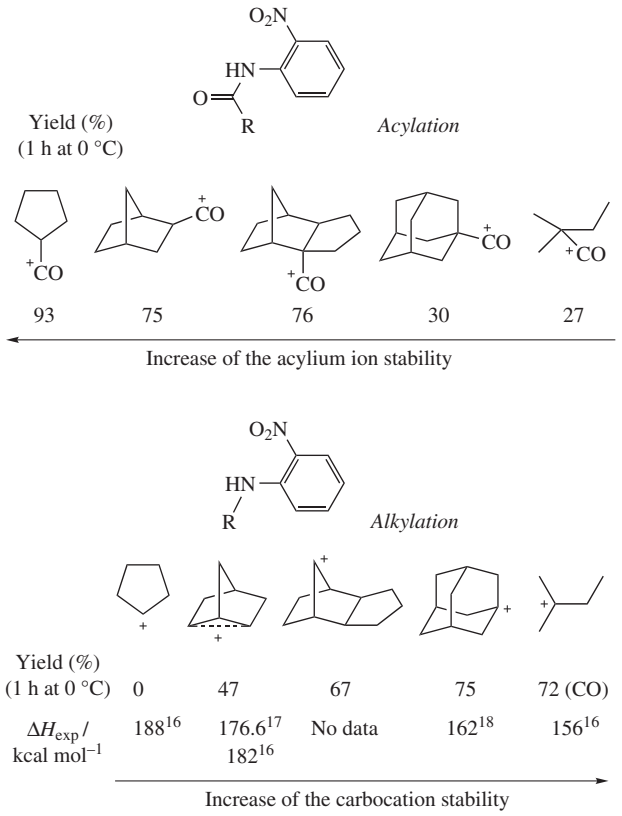
Scheme 3

change in the reaction conditions (see entries 18 and 21 in Table 1) led to nonselective alkylation resulting in three isomeric alkylation products. Using different precursors of the trimethylenenorbornyl cation in the Ritter reaction with acetonitrile initiated by BF_3 in liquid SO_2, Bakke and Knudsen obtained amide (**2**, R = NHCOMe) in 95% selectivity, while amides **3** were the main products in similar reactions with other nitriles and electrophiles.[13] The formation of less stable isomers **2** (R = $NHC_6H_4NO_2$, NHCOMe) is probably due to both a large flexibility of the trimethylenenorbornyl group and a low difference between the stabilities of cations **1′** and **2′** (~4.8 kcal mol[†] compared with the values of 9–12 kcal mol^{-1} for tertiary and secondary alkyl cations[14]).

Surprisingly, the treatment of the *in situ* generated *tert*-$C_5H_{11}CO^+$ with nitroaniline under CO atmosphere at 35 °C for 1 h or at 20 °C for 12 h afforded an alkylation product, *tert*-$C_5H_{11}NHC_6H_4NO_2$, in 87 or 72% yield, respectively, while the yields of the expected acylation product, *tert*-$C_5H_{11}CONHC_6H_4NO_2$, were only 13–27%. In the absence of CO, both reactions of nitroaniline with *n*-pentane and *tert*-$C_5H_{11}CO^+$ were inefficient and nonselective. In other words, a high yield of the alkylation product with *n*-pentane can be achieved if the acylium cation instead of alkane is used as the precursor of the *tert*-amyl cation. Thus, the role of CO, which, obviously, does not participate in the formation of alkylation products, is very important. We believe that the effect of CO consists in the maintaining low concentration of the amyl cations in the media. As the result, the alkylation of nitroaniline occurs, probably, rather than alkylation of conjugated olefins with the amyl cation resulting in the formation of oligomers and fragmentation products. The presence of CO may be important for other reactions with the participation of cations that are prone to cracking.

Generally, the yields of the acylation products increase with growing stabilities of corresponding acylium cations.[15] Similarly, the yields of the alkylated products increase with growing stabilities of the corresponding carbocations. Scheme 4 shows a reasonable correlation between the yields of acylation and alkylation products and stabilities (enthalpies) of the corresponding acylium cations and carbocations. Cyclopentane generating the less stable carbocation among the above listed displayed the maximal activity in acylation and the absence of activity in alkylation. The enthalpy of the norbornyl cation[17] seems more realistic than that presented by Steward.[16] The former data shows

[†] The B3LYP/6-31** calculations by N. P. Gambaryan. Moscow, INEOS, unpublished data.



Scheme 4

that this nominally secondary ion, but in fact non-classical cation[19] is unusually stable (11.4 kcal mol^{-1} more stable than the cyclopentyl cation). Adamantane producing the second on stability carbocation after *n*-pentane showed the record-breaking activity in alkylation; *n*-pentane generating a thermodynamically stable but kinetically labile cation formed N-alkylation product in a high yield in the presence of CO only. However, surprisingly, the difference between the enthalpies of cyclopentyl and norbornyl cations is relatively small while the yields of the alkylation reactions changed dramatically.

Thus, the first selective one-pot N-alkylations and N-acylations of a weak nucleophilic substrate, *o*-nitroaniline, with saturated hydrocarbons were performed, and a correlation between the activities of RH in both of the reactions and the stabilities of corresponding RCO^+ and R^+ cations was demonstrated. The alkylation with *n*-pentane was effective if the acylium cation rather than alkane served as the precursor of the *tert*-amyl cation.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2010.09.005.

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