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Propargyl Bromide as an Excellent α-Bromoacetone Equivalent: Convenient and New Route to α-Aroylacetones†

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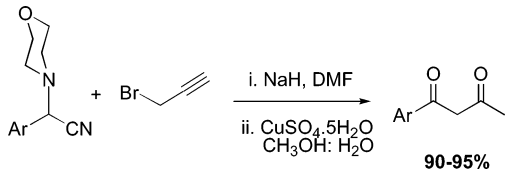
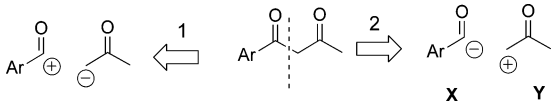
Received July 24, 2005



A variety of α-aroylacetones **4a**−**g** have been prepared in excellent yields following a new protocol wherein α-aminonitriles **1a**−**g** as the aryl acyl anion equivalents readily react with propargyl bromide as the α-bromoacetone equivalent. The alkylated product undergoes one-pot unmasking of the keto functionality along with Markovnikov's hydration of the terminal alkyne with $CuSO_4 \cdot 5H_2O$ in aqueous methanol at 60 °C to furnish the desired target in excellent isolated yields.

β-Diketones have been important intermediates in organic synthesis since the discovery of the Claisen condensation more than a century ago.[1a−j] They have served as key building blocks in the preparation of heterocyclic compounds such as pyrazoles,[1k] isoxazoles,[1l] triazoles,[1m] and benzopyran-4-ones.[1n,o] Their use as chelating ligands for lanthanides and transition metals has been equally prominent.[1p] The most familiar and general strategy for β-diketone functionality is based on disconnection 1 and involves either (i) the acylation of the ketones with acyl halides[2a−d] or (ii) the acylation of acetylacetone followed by base, which promotes deacetylation.[3a−c] On the basis of this concept, α-aroylacetones in particular have been synthesized. However, the anion from acetylacetone, being ambident, causes the reaction with the acylating agent to often be plagued by the possibility of C and/or O acylation. Besides the structural influence of the starting substrates, a very delicate control over the nature of the solvent, the electrophile, the metal counterion, and the reaction temperature has to be maintained for any observable chemoselectivity to occur. Presently, 1-aroylbenzimidazoles[4] and 1-aroylbenzotriazole[5] have been used for the aroylations of the anion from acetylacetone and the subsequent obtainment of the desired targets. A moderate yield (26−30%) has been observed with the former, whereas the latter, due to Katritzky, has furnished excellent yields (52−100%) as a result of greatly reduced O acylation. To the best of our knowledge, disconnection 2, envisaging the use of the arylacyl anion, has never been explored toward this end. Because there is no dearth of acyl anion equivalents in the literature,[6] the route appeared highly attractive. Herein, we report the success of this new route based on disconnection 2.



From the plethora of reagents available for the acyl anion synthon **X**, we were attracted by the less frequently used α-aminonitriles **1** as a result of the simplicity and convenience involved in their preparation on the multigram scale.[7] Also, unlike alkylations of other acyl anion equivalents that require much stronger bases, stringent dry conditions, and low temperatures, the alkylation of α-aminonitriles is conveniently carried out at room temperature.[8a,b] The carbanion from the α-aminonitriles (**1a**−**g**), generated using NaH in DMF, underwent clean and facile quantitative alkylation with propargyl bromide **2** (Scheme 1). The progress of the reaction could be easily seen

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† This paper is dedicated to Professor N. S. Narasimhan.

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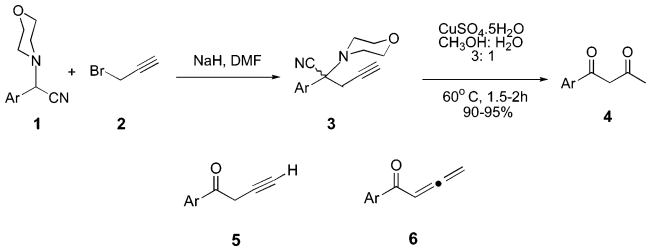
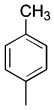
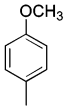
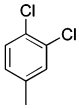
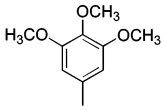
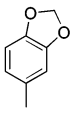
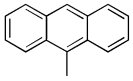
10.1021/jo051538w CCC: $33.50
Published on Web 11/24/2005

SCHEME 1



by the gradual decrease of the yellow color of the carbanion. The formation and obtainment of the alkylated product **3a** in quantitative yield after the standard workup and purification was confirmed by ^{1}H NMR. The two protons from the methylene unit of the propargyl residue were diastereotopic in nature and appeared as a mutually coupled doublet of doublets, one centered at δ 3.43 and the other centered at 3.56 with $J = 16.6$ and 2.5 Hz. The alkynic proton appeared as a triplet at δ 2.62 with $J =$ 2.5 Hz. Purified **3a** and the other alkylated products **3b**−**g**, without any purification, were directly subjected to hydrolysis using $CuSO_4 \cdot 5H_2O$ in aqueous methanol at 60 °C for unmasking of the carbonyl group.[9] However, gratifyingly, these reaction conditions resulted in both the clean unmasking of the keto functionality along with the conversion of the propargyl residue to the acetonyl unit and, thereby, furnishing α-aroylacetones **4a**−**g** in excellent yields (90−95%; Table 1). Apparently, the hydration of the terminal alkyne in the Markovnikov's fashion would explain the formation of the acetonyl unit. However, mechanistically, the isomerization of the acetylenic ketone **5** to the allenic ketone **6** under the reaction conditions described and the subsequent addition of water in Michael fashion to arrive at the obtained product cannot be ruled out. It is worth noting that, with the successful formation of the α-aroylacetones, propargyl bromide has surfaced as an elegant equivalent to the sensitive α-bromoacetone or the carbonyl-protected α-bromoacetone that otherwise one would have used for the implementation of the unexplored strategy. If Markovnikov's hydration of the terminal alkyne is operating, the successful use of $CuSO_4 \cdot 5H_2O$ would be worth noting. Toward this end, several other inorganic salts, either in stoichiometric or in catalytic amounts, have been used; however, the use of the Cu(II) species has not been reported.[10] The structures of known products **4a**,[4,11] **4b**,[4] **4c**,[4] **4d**,[12] **4e**,[13] **4f**,[14,15] and **4g**[16] are supported by microanalysis and ^{1}H/^{13}C NMR data, which show ^{1}H singlets between δ 6.04−6.54 corresponding to the α-olefinic protons and signals at δ 92.5−96.7 in the ^{13}C NMR spectrum for the α-olefinic carbons. All of the β-diketones **4a**−**g** contained the corresponding keto forms as minor tautomers. The minor keto structures were characterized by ^{1}H singlets between δ 3.99−4.45 and by ^{13}C NMR signals between δ 48.3−55.1, and the relative amounts were estimated by ^{1}H NMR.

TABLE 1. Products Obtained after Hydrolysis of Alkylated Intermediates 3a−g Using $CuSO_4 \cdot 5H_2O$, CH_3OH/H_2O (3:1) at 60 °C

Products	Aryl	Time (h)	Yield (%)[a] (Keto+enol)	Enol (%)[b]
4a		1.5	92	85
4b		1.5	90	83
4c		1.5	90	92
4d		1.5	95	87
4e		2	92	76
4f		2	90	86
4g		2	91	83

[a] Isolated yields of the products which were recovered as mixtures of the keto−enol tautomers evidenced by ^{1}H NMR in $CDCl_3$. [b] Determined by ^{1}H NMR of product **4**.

In conclusion, quantitative propargylation of α-aminonitriles as aryl acyl anion equivalents, followed by the one-pot unmasking of the keto functionality along with the hydration of the terminal alkyne in excellent yield, has provided a completely new and highly convenient protocol for α-aroylacetones hitherto unreported in the literature.

Experimental Section

The starting α-aminonitriles **1a**−**f** were prepared using the literature procedure.[7] The unreported α-aminonitrile **1g** was prepared using the same protocol and was fully characterized before use.

General Procedure for the Preparation of α-Aroylacetones 4a−**g.** To a suspension of sodium hydride (1.2 mmol) in dry DMF (1 mL) under an inert nitrogen atmosphere was added a solution of the α-aryl aminonitrile (**1a**−**g**; 1.1 mmol) in dry DMF (3.5 mL) in a dropwise manner at room temperature (ca. 27−30 °C). After stirring the reaction mixture for 30 min at room temperature, a solution of the propargyl bromide **2** (1 mmol) in dry DMF (3.5 mL) was added dropwise. The reaction mixture was stirred for an additional 1 h at room temperature to ensure the completion of the reaction. After the completion of the reaction, saturated ammonium chloride solution (10 mL) was added. The aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined dichloromethane layer was dried over anhydrous sodium sulfate and evaporated to obtain the alkylated compound (**3a**−**g**), and the residue was directly subjected to hydrolysis. To a solution of $CuSO_4 \cdot 5H_2O$ (2 mmol) in CH_3OH/H_2O (3:1, 12 mL) was added the alkylated compound (**3a**−**g**; 1 mmol), and the contents were

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heated at 60 °C. After 1.5 h, the solvents were evaporated on a rotary evaporator, and to the residue was added water (10 mL). The aqueous layer was extracted with dichloromethane (3 × 10 mL), and the combined organic layer was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the product was purified by silica gel column chromatography (hexane/ethyl acetate, 9:1), affording the α-aroylacetone (**4a**−**g**) in excellent yield (90−95%).

Acknowledgment. We thank CSIR, New Delhi, for the funding of the new project in the year 2005 [01(1971)/05/EMR-II]. We thank DST, New Delhi, for the funding toward the 400-MHz NMR instrument under the IRPHA scheme and the ESI-MS facility under the DST-FIST program. S.M.M. is thankful to IIT-Madras for the fellowship.

Supporting Information Available: General methods, ^{1}H and ^{13}C spectra of compounds **3a**,**b** and **4a**,**b**,**e**, DEPT experiment of compound **4a**, and HRMS spectra of compounds **3a** and **4b**,**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO051538W